VOLUME 20 August, 1954 NUMBER 8

THE AMERICAN SURGEON

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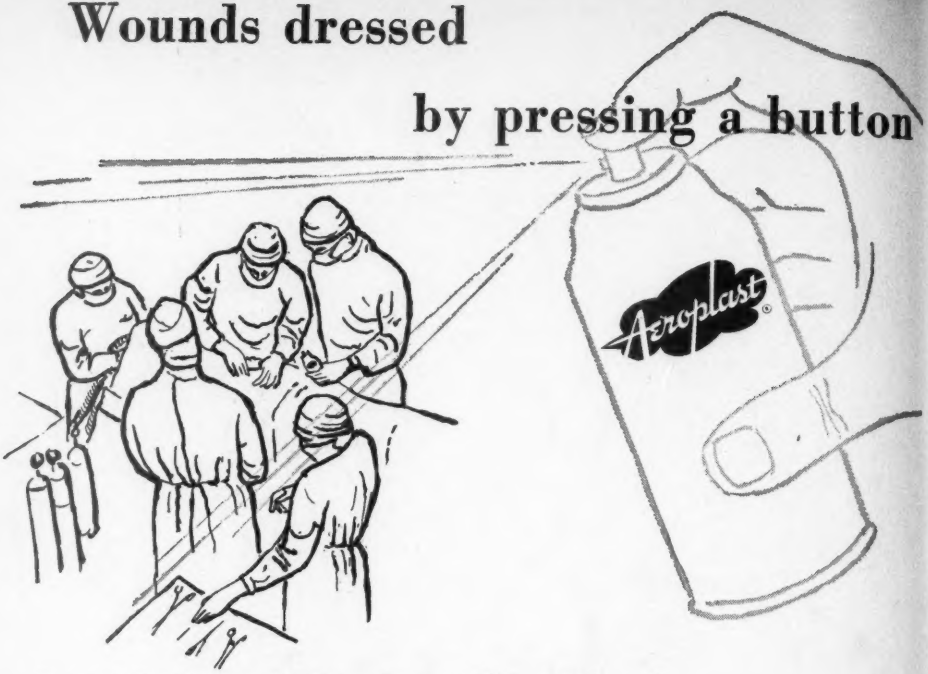

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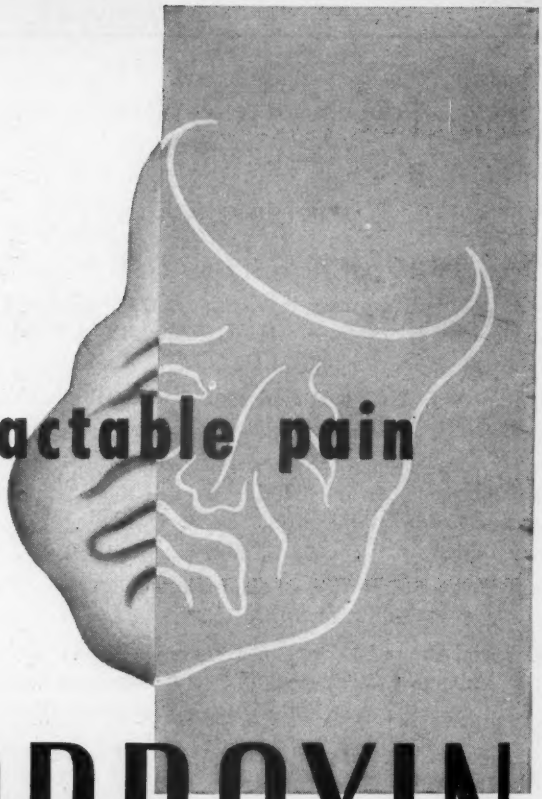

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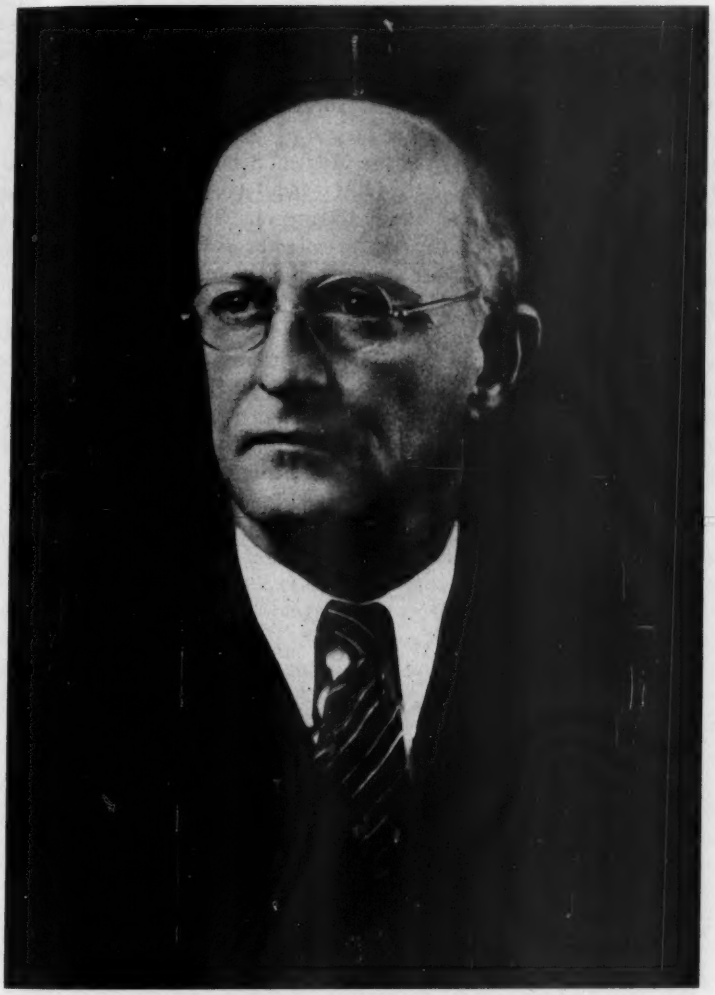

BARNEY BROOKS, M.D.

Former Professor of Surgery and Head of the Department of Surgery, Vanderbilt University School of Medicine, Nashville, Tennessee

Barney Brooks was born in Jacksboro, Texas, Dec. 17, 1884, the son of James Standifer and Emma Jane Holmes Brooks. He died at the Vanderbilt University Hospital in Nashville, Tennessee, March 30, 1952. In the 67 years of his life he became a devoted husband and father, a responsible citizen, a distinguished surgeon, a productive investigator and an exceptionally effective teacher.

Dr. Brooks' early experiences at the Johns Hopkins Medical School and Hos-

pital with Dr. William S. Halsted and at the Washington University School of Medicine and the Barnes Hospital with Dr. Ewarts Graham were but preparatory to his last and most important assignment. In 1925 he became Professor of Surgery and Head of the Department of Surgery of the reorganized Vanderbilt University School of Medicine. Here his talents came into full maturity. He created a Department of Surgery in the Medical School and a training and research program in the University Hospital which have contributed importantly to the education and training of American surgeons. The pattern of his unique performance in the roles of teacher and investigator as well as his actual accomplishments will interest and inspire students of medicine for years to come. His career already has become legendary at Vanderbilt.

This number of THE AMERICAN SURGEON is the product of members of the surgical faculty at Vanderbilt, many of whom were Dr. Brooks' former house officers. It is dedicated by them to their former Chief. Here, from but a few of his old students, is convincing affirmation of the enduring value of his teaching and his practice. It is also an altogether appropriate tribute to him from some of the people he judged to be the most important in his life.

HUGH J. MORGAN, M.D.
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THE
AMERICAN
SURGEON

Vol. 20, No. 8 August, 1954

HYPOTHERMIA AS AN ADJUVANT IN CARDIOVASCULAR SURGERY: EXPERIMENTAL AND CLINICAL OBSERVATIONS

H. William Scott, Jr., M.D.,* Harold A. Collins, M.D.,†
John H. Foster, M.D.‡

Nashville

Although numerous investigators[2, 23, 26] have studied the application of local and generalized cooling in a variety of conditions, the credit for envisioning the use of generalized hypothermia as an adjuvant in cardiovascular surgery belongs to Bigelow.[6] He and his associates have demonstrated that the oxygen demands of heart muscle and other tissues are reduced proportionally with lowering of body temperature. As body temperature falls, arterial pressure, pulse rate and cardiac output are reduced. It has been shown by Bigelow,[6] Lewis,[18] Boerema,[9] Swan[25] and their respective associates in laboratory experiments that tolerance to temporary interruption of the venous return to the heart is extended significantly by hypothermia.

As Bigelow[6, 7] has suggested, the reduction in metabolic rate afforded by hypothermia offers an approach to intracardiac surgery which serves as an alternative to the more complicated methods involving an extracorporeal circulation with a mechanical pump-oxygenator. In the last two years Bigelow's basic work and concepts have been extended and applied clinically by Lewis,[18] Swan,[24] Bailey[5, 13] and their associates, and other groups interested in cardiovascular surgery. Both experimental and clinical achievements have been noteworthy. Atrial septal defects have been closed successfully under direct vision using simple suture methods by both Lewis and Swan. Bailey has been able to close a defect in the interventricular septum in the same manner. Swan has relieved the obstruction in both infundibular and valvular forms of pulmonic stenosis under direct vision.

Much practical information has been derived from animal studies as regards the application of hypothermia in patients with cardiovascular problems. It has

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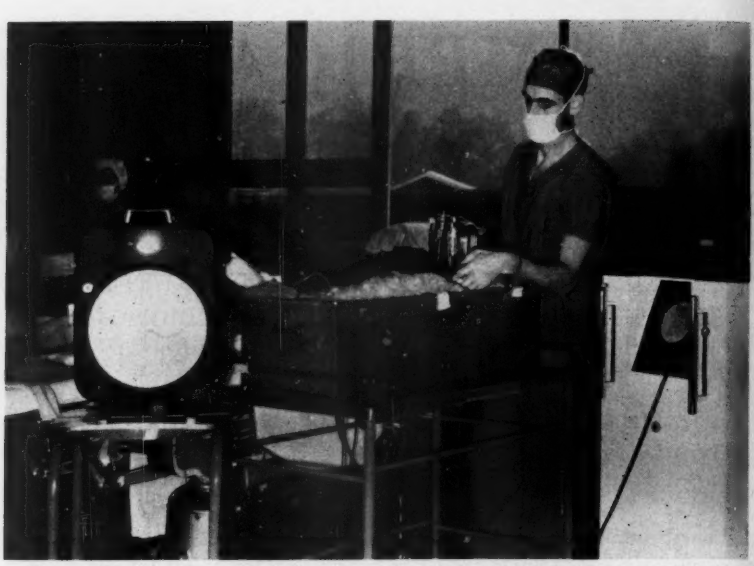

FIG. 1. Small tank used to induce hypothermia in infants and young children

been our interest to continue explorations along these lines in the laboratory. At the same time we have attempted to assess the clinical value of hypothermia by using it primarily in poor-risk cyanotic infants with severe forms of congenital pulmonary stenosis and in other patients with cardiac disease in whom a grave danger of myocardial anoxia during operation has been anticipated. Our initial experimental and clinical experience with hypothermia forms the basis of this report.

METHODS OF PRODUCTION OF HYPOTHERMIA

There are a variety of methods for producing a generalized reduction in body temperature. These include the use of refrigerated blankets, immersion in ice water, packing in crushed ice either applied directly or in plastic bags, and the use of a *deep-freeze* type of cold chamber. The body temperature may be lowered efficiently by circulating the patient's blood through an extra-corporeal system of tubes exposed to a refrigerating unit.[14] Various drugs, including chlorpromazine, which apparently act directly on the thermal center, have been used to facilitate the induction of hypothermia, usually for surgical purposes in combination with some physical method of chilling.[21] Induction of anesthesia prior to the exposure to cold is believed to be essential, not only for the subject's comfort, but also to prevent shivering which retards temperature reduction.

There are various disadvantages to each of the several methods for induction of hypothermia. The cold chamber method is awkward for operating room use and apparently is apt to produce frostbite.[5] The refrigerated blankets are relatively slow and inefficient in lowering body temperature as compared to the procedure of packing the subject in crushed ice or immersion in ice water. The latter method which is advocated by Swan[24] has the advantages of simplicity, efficiency, and economy and is the technic which we now have adopted for both laboratory and clinical use. A small tank, 9 by 13 by 36 inches in size is satisfactory for infants and young children (fig. 1) while an ordinary bathtub mounted on a dolly to facilitate use in the operating room is useful for older children and adults (fig. 2).

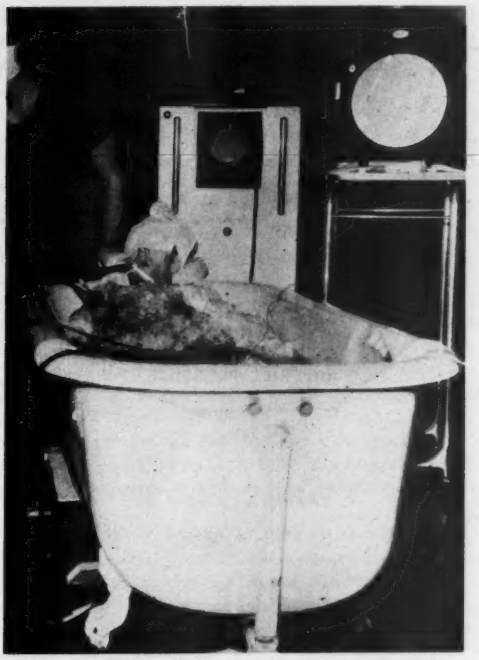

FIG. 2. Induction of hypothermia in an adult

After the induction of anesthesia the patient is immersed in the ice water bath and remains in it until body temperature is lowered to the desired range. He is then removed from the bath to the operating table; placed in the proper position; prepared, draped and subjected to operation. After the completion of the operative procedure, the wound is sealed with collodion and the patient is lifted from the operating table and immersed in a tub of warm water (42 C. to 44 C.) where he remains until his temperature has returned to a normal level.

The same tank or tub which is used for cooling is used for the rewarming procedure. A continuous recording of rectal temperature is essential during the period of cooling, the course of operation and the time of rewarming. Similarly, a continuous electrocardiographic monitoring of cardiac activity is desirable. Figure 3 shows the changes in temperature, pulse rate and arterial pressure in an operative procedure carried out under hypothermia induced by immersion in ice water and followed by rapid rewarming.

EXPERIMENTAL OBSERVATIONS

Our objectives in the study of hypothermia in the experimental surgical laboratory have been to assess the practical advantages and limitations of the modality of cold when used in combination with temporary interruption of the cardiac venous inflow as a means of carrying out brief intracardiac procedures under direct vision in a dry field. Bigelow[8] has shown that the oxygen consumption in dogs at 26 C. is only 40 per cent of that at 37 C. Gollan[17] and others have demonstrated that the tendency to fatal ventricular fibrillation is enhanced in the dog at temperatures much below 25 C. In consequence, our studies have been made in animals cooled to a range of 25 C. to 27 C. We have specifically attempted in

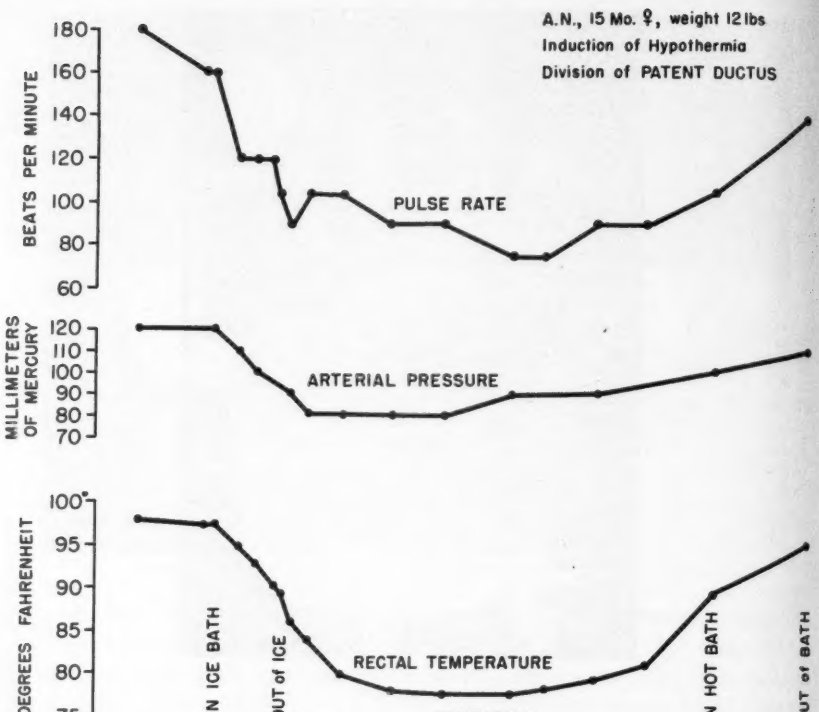

FIG. 3. Graph depicting changes in pulse rate, blood pressure and temperature during operation under hypothermia.

these experiments to determine the value of hyperventilation as a means of reducing the incidence of fatal ventricular fibrillation in hypothermic dogs subjected to cardiac inflow stasis[25] and to evaluate the method of outflow stasis advocated by Lewis and Taufic[18] and by Swan[25] as a means of preventing coronary air embolism during open heart surgery under hypothermia.

Methods

Adult mongrel dogs were used in these experiments. Anesthesia was produced by the intravenous administration of pentobarbital (30 mg. per Kg. of body weight). The animals then were clipped closely. An endotracheal tube was inserted and respiration maintained by a mechanical insufflator attached to an oxygen tank with an oxygen flow of 6 to 8 liters per minute. Catheters were inserted into the femoral artery for the recording of blood pressures and into the inferior vena cava through the femoral vein for the periodic withdrawal of blood samples. Each animal then was placed into a tub of ice water at 0.5 C. to 1.0 C. When the animal's temperature had fallen to 29 C. to 30 C. as recorded by a thermometer inserted 10 cm. into the rectum, he was removed from the ice water. The animal then was prepared for operation.

Thoracotomy was done aseptically in all animals through the right fourth intercostal space. The superior and inferior venae cavae and the azygos vein were dissected free and ligatures placed loosely about them. In experiments with outflow stasis these veins were occluded simultaneously while pulmonary insufflation was discontinued. One minute after the venous occlusion a noncrushing clamp was applied through the opened pericardium to the aorta and pulmonary artery at the base of the heart, low enough to occlude both of these vessels and the coronary arteries. When cardiotomy was done, the right atrium was incised longitudinally. When an interatrial septal defect was to be produced, a portion of the septum approximately 2 cm. in diameter was excised 1 cm. above and 1 cm. posterior to the coronary sinus. This defect then could be sutured with a continuous silk suture. Air was evacuated from the heart by instilling saline into the open atrium following which the atrial incision was closed with a continuous mattress suture of silk returned on itself as an over and over suture. After the lapse of the specified time planned for inflow stasis in each group of experiments, the ligatures about the superior vena cava and azygos vein were released while pulmonary ventilation was reinstituted. About one minute later the ligature about the inferior vena cava gradually was released. In experiments with outflow stasis the clamp occluding aorta and pulmonary artery was removed simultaneously with release of the superior vena cava.

After loosely closing the pericardium the lungs were re-expanded and the chest closed in layers. Each animal was then immersed in a tank of warm water at 42 C. to 44 C. until the body temperature had returned to 37 C. Penicillin and streptomycin usually were given postoperatively.

The various experiments which were done may be divided into two groups. In Group A the value of hyperventilation in hypothermia was assessed by comparing the tolerance to cardiac inflow stasis for periods of 10, 15 and 20 minutes in one group of dogs without hyperventilation (respiratory rate 18 to 20 per minute) with the tolerance to inflow stasis for similar periods in another group of dogs with hyperventilation (respiratory rate 40 to 60 per minute). Auricular cardiotomy was done in 21 of the 37 dogs and in 7 of the hyperventilated animals excision and immediate suture of the atrial septum was done in addition.

In Group B a comparison was made of the tolerance to cardiac inflow and outflow stasis in one group of animals for a 10 minute period with the tolerance to inflow and outflow stasis for a 6 minute period in another group. All Group B animals were hyperventilated and in all but 2 an auricular cardiotomy was done.

Results

In general most of the animals which survived operation and the immediate postoperative period remained healthy and active. Animals surviving for a month or more were killed or used for other studies in the laboratory.

Using the routine laboratory dose of pentobarbital (30 mg. per kg.) little or no shivering has occurred during the cooling procedure. When hypothermia is induced by immersion in ice water, it requires only 15 to 25 minutes for the average dog's body temperature to reach 29 C. to 30 C. This method may be contrasted with an earlier method of cooling used in this laboratory which consisted of packing ice in plastic bags about the animal, a technic requiring 45 to 60 minutes to produce the same degree of cooling. It has been consistently observed in these experiments, as noted by others, that following removal from the ice bath the animal's temperature further decreases by 5 to 7 degrees centigrade. The temperature then remains fairly stable for one to two hours, following which it very slowly starts rising toward normal.

Rewarming by immersion in warm water usually requires a slightly longer period of time than does the cooling process. This is probably attributable to the

fact that the differential between body temperature and warming temperature is not as great as that between body temperature and cooling temperature. We have thought that it has been advantageous to produce rewarming as rapidly as possible but have no objective evidence to substantiate this belief.

Group A Experiments: Thirty-seven dogs were used in this group of experiments. All were cooled as described above to a range of 25 C. to 27 C.

In 16 animals the respiratory rate during cooling and operation was maintained at 18 to 20 per minute. In 6 of these dogs inflow stasis alone was produced for 20 minutes with 3 survivors and 3 deaths from ventricular fibrillation. In 5 others inflow stasis alone was produced for 15 minutes with 3 survivors and 2 deaths from ventricular fibrillation. In the remaining 5 animals inflow stasis was produced for 10 minutes and the right atrium was opened widely, filled with saline, and sutured. Four of these animals died during or immediately after operation of ventricular fibrillation or cardiac arrest. One dog survived operation but died the following day with extensive gangrene of the small bowel of unknown cause. Thus, 9 of these 16 dogs died with irreversible cardiac arrest or ventricular fibrillation at or immediately after operation despite extensive resuscitative efforts including the use of prolonged cardiac massage, repeated electric shock, and the serial use of potassium chloride and calcium chloride as suggested by Swan.[25]

In 21 animals the respiratory rate during cooling and operation was maintained at 40 to 60 per minute. Cooling was carried out as above to the range of 25 C. to 27 C. In 5 of these dogs inflow stasis alone was produced for 15 minutes. All animals survived and ventricular fibrillation did not occur in any of them. In 9 of the dogs inflow stasis was produced for 10 minutes and right auricular cardi-

TABLE I
THE VALUE OF HYPERVENTILATION IN HYPOTHERMIA

PROCEDURE	NUMBER OF ANIMALS	DIED	SURVIVED	% SURVIVING
WITHOUT PRIOR HYPERVENTILATION:				
20 MINUTE INFLOW STASIS	6	3	3	50%
15 MINUTE INFLOW STASIS	5	2	3	60%
10 MINUTE INFLOW STASIS and RIGHT AURICULAR CARDIOTOMY	5	4	1	20%
TOTAL	16	9	7	43.7%
WITH PRIOR HYPERVENTILATION:				
15 MINUTE INFLOW STASIS	5	0	5	100%
10 MINUTE INFLOW STASIS and RIGHT AURICULAR CARDIOTOMY	9	2	7	77.7%
10 MINUTE INFLOW STASIS and PRODUCTION and REPAIR of INTRATRIAL SEPTAL DEFECT	7	2	5	71.4%
TOTAL	21	4	17	80.9%

TABLE II

TOLERANCE to CARDIAC INFLOW and OUTFLOW STASIS DURING HYPOTHERMIA*

PROCEDURE	NUMBER OF ANIMALS	DIED	SURVIVED	% SURVIVING
10 MINUTE INFLOW-OUTFLOW STASIS+	14	12	2	14.3%
10 MINUTE INFLOW STASIS°	16	4	12	75 %
6 MINUTE INFLOW-OUTFLOW STASIS×	5	1	4	80 %

* ALL ANIMALS HAD HYPERVENTILATION BEFORE and DURING OPERATION.
+ ALL BUT TWO HAD RIGHT AURICULAR CARDIOTOMY.
° ALL HAD RIGHT AURICULAR CARDIOTOMY and SEVEN HAD SEPTAL DEFECT PRODUCED and REPAIRED.
× ALL HAD RIGHT AURICULAR CARDIOTOMY.

otomy was done. There were 7 survivors and 2 deaths, 1 from ventricular fibrillation and the other from a technical error. In 7 other dogs of the hyperventilation group inflow stasis was produced for 10 minutes while excision and suture of the interatrial septum was done. There were 5 survivors and 2 deaths—1 from ventricular fibrillation and 1 from a technical error. Thus, only 2 of the 21 dogs in which hyperventilation was used succumbed to ventricular fibrillation. In table I these data are summarized.

Group B Experiments: Nineteen dogs were used in this group of experiments. All were cooled as detailed above to a range of 25 C. to 27 C. and hyperventilation (respiratory rate 40 to 60 per minute) was maintained in each instance during cooling and operation.

In 14 dogs both inflow and outflow stasis were produced for 10 and 9 minutes respectively. In 2 of these animals nothing else was done while in the remaining 12 dogs an auricular cardiotomy was carried out. Eleven of the 14 dogs died during operation with irreversible ventricular fibrillation and 1 other animal died suddenly five hours after operation; no cause for death could be found at autopsy in this animal. Two dogs survived the procedure.

In 5 animals both inflow and outflow stasis were produced for six and five minutes respectively while an auricular cardiotomy was done. There were 4 survivors and 1 death from ventricular fibrillation. These data are summarized in table II.

CLINICAL EXPERIENCES

During the last year hypothermia has been used as an adjuvant to cardiovascular surgery in 11 patients with congenital heart disease at the Vanderbilt University Hospital. Each of these patients was considered to be an extremely poor surgical risk in whom the probability of surviving operation seemed slight. Ages ranged from 3½ months to 30 years but most patients were infants or very young children with severe manifestations of congenital pulmonary stenosis. In 9 cases hypothermia was used to reduce oxygen demands during extra-cardiac operative procedures and in two instances hypothermia was used to permit stasis cardioto-

mies with intracardiac maneuvers under direct vision. Brief case summaries follow:

Case 1. D. C. (This case has been previously reported[12]). The patient was a 4½ month old white male with the presumptive diagnosis of tetralogy of Fallot. Severe episodes of cyanosis, dyspnea and syncope made operation mandatory. Operation was done May 1, 1953. Anesthesetic induction was with cyclopropane anesthesia. Ice contained in plastic bags was packed about the infant. The rectal temperature decreased from 37 C. to 28 C. in 34 minutes, at which time the ice was removed. There was no apparent cyanosis at this temperature. An end to side anastomosis between left subclavian and left pulmonary arteries was then made. There were sporadic episodes of premature ventricular contractions during operation. At the conclusion of the operation the rectal temperature was 29 C. The infant was placed immediately in a water bath at 40 C. and 40 minutes later, when his rectal temperature had reached 35 C., he was removed. The postoperative course was essentially uneventful until the sixteenth postoperative day when he was observed to have multiple indurated, tender subcutaneous nodules. Upon biopsy these proved to be subcutaneous fat necrosis. By the twenty-sixth postoperative day these lesions had almost disappeared and the child was discharged. On the thirty-first day after operation the child died of unknown causes in another hospital. Permission for an autopsy could not be obtained.

Case 2. G. D. This was a 14 month old white male with congenital cyanotic heart disease. He had frequent episodes of profound cyanosis associated with unconsciousness. Physical examination disclosed a 15 pound infant who appeared malnourished. He was cyanotic at rest. There was a blowing systolic murmur along the left sternal border. Cardiac catheterization findings were compatible with the diagnosis of the tetralogy of Fallot. Chest fluoroscopy demonstrated a right-sided aorta. The heart had a suggestively boot-shaped configuration. An electrocardiogram was interpreted as showing sinus tachycardia and right ventricular preponderance. It was thought that operation was indicated because of the gravity of this child's condition. Operation was done on July 20, 1953. After induction of anesthesia, cooling was accomplished by placing polyethylene ice bags about the child. The rectal temperature decreased from 37 C. to 28 C. in 31 minutes, at which point the ice was removed. A left subclavian pulmonary end to side anastomosis was made. There were occasional premature ventricular contractions during the operative period, at the conclusion of which the rectal temperature was found to be 26 C. The child was placed in a water bath at 42 C. and within 50 minutes the rectal temperature was 35 C. Immediately postoperative he did well except for mild pharyngitis. He has continued to be mildly cyanotic although his exercise tolerance has increased and there have been no further episodes of unconsciousness.

Case 3. R. B. This 18 month old white female had the tetralogy of Fallot with severe cyanosis and attacks of syncope. Operation was done Aug. 7, 1953. Anesthetic induction was with cyclopropane. Ice in plastic bags was placed about the patient, and the rectal temperature decreased from 38 C. to 28 C. in 40 minutes, at which time the ice was removed. There was a remarkable disappearance of cyanosis. An end to side anastomosis between the right subclavian and right pulmonary arteries was done. During operation there was no abnormality of cardiac rhythm. At the conclusion of the operation, the rectal temperature was 28 C. The child was placed in a water bath at 41 C., and the rectal temperature had reached 35 C. in 45 minutes. Postoperatively there were no complications. On a return visit to the cardiac clinic Sept. 27, 1953, the parents stated that the child had had *knots under her skin* two weeks previously. This had been confirmed by the family physician, but there was no apparent abnormality at the time of the clinic visit. It is impossible to state categorically whether or not this represented subcutaneous fat necrosis. The operative result has been good.

Case 4. J. G. This 23 year old white woman had the tetralogy of Fallot. In March 1953 thoractomy was done and infundibular stenosis found. Infundibulectomy was performed at this time. During ensuing months the patient experienced little symptomatic improvement. She continued to be cyanotic and to have greatly reduced exercise tolerance. On

readmission in September 1953 she was found to have auricular flutter. Under hypothermia a left subclavian pulmonary end to side anastomosis was made. With ice in plastic bags placed about the patient, it required two hours to reduce the temperature from 37 C. to 29 C. During operation the ventricular rate slowed to 18 to 20. At the conclusion of the operation the rectal temperature was 25 C. It required two hours in a water bath at 45 C. to raise the rectal temperature to 36 C. Sinus rhythm was restored during rewarming. It is noteworthy that in this adult there was little detectable change in cyanosis during the hypothermia. Her improvement since operation has been very gratifying.

Case 5. G. K. This 2½ year old white girl was diagnosed as having a tetralogy of Fallot. Operation was done Nov. 4, 1953. The rectal temperature was reduced from 37.5 C. to 30 C. in 26 minutes by placing her in a tub of ice water. After removal, the temperature further decreased to 25.5 C. An end to side anastomosis between left subclavian and pulmonary arteries was made. During operation there was an idioventricular rhythm. At the conclusion of the operation, the temperature was 26.5 C. She was placed in a water bath at 45 C. and in 35 minutes the temperature had reached 35 C. She has been greatly improved since operation.

Case 6. J. L. This 30 year old white man was operated upon under hypothermia on Nov. 20, 1953, with the presumptive diagnosis of aortico-pulmonary fistula. Preoperative studies had shown extreme pulmonary hypertension, aneurysmal dilatation of the pulmonary artery and evidence of reversal of flow through the aortic-pulmonary shunt. Rectal temperature was reduced from 37 C. to 30 C. in 48 minutes by placing the patient in ice water. The temperature further decreased to 28 C. during operation. A patent ductus arteriosus 27 mm. in diameter was found at operation. After division of the ductus arteriosus, cardiac arrest occurred and could not be reverted. It was thought that the hypothermia played no role in the cardiac arrest which was probably due to acute cor pulmonale.

Case 7. S. C. Tetralogy of Fallot was the presumptive diagnosis in this 3½ month old white male who had severe cyanosis and prolonged attacks of syncope. Operation was done Dec. 18, 1953, under hypothermia. After being placed in an ice water bath, his rectal temperature decreased from 35 C. to 30 C. in 12 minutes. Following removal from the ice water the temperature further decreased to 25 C. A Potts anastomosis was made without incident. The rectal temperature increased from 26 C. to 35 C. in 30 minutes with the child in a water bath at 44 C. There was no significant electrocardiographic abnormality during operation. The postoperative result has been excellent.

Case 8. H. W. This 4 year old white boy with great cardiac enlargement and incapacity had a presumptive diagnosis of interatrial septal defect. He was subjected to operation on Jan. 8, 1954. Rectal temperature was reduced from 36 C. to 28 C. in 30 minutes by placing the patient in a bath of ice water. The temperature further decreased to 23 C. after removal from the bath. Bilateral anterior thoracotomy was done, the venae cavae were isolated and ligatures placed loosely about them. The azygos vein was ligated. The pericardium was opened widely. The venae cavae were then occluded. One minute later a clamp was placed across the base of the pulmonary artery and the aorta so that the coronaries were occluded. The right atrium was incised. A large defect at the annulus of the tricuspid valve was presumed to be an interatrial defect of the ostium primum variety and was closed with a continuous no. 000 silk suture. The chest was then flooded with saline and the auricular incision occluded with clamps. The clamp across the pulmonary artery and aorta was removed and the superior vena cava was released. (Period of inflow stasis was 11 minutes and outflow stasis 10 minutes.) Cardiac action was weak and the heart was massaged a few times. Ventricular fibrillation immediately supervened and could not be reverted satisfactorily. At autopsy air was found in the coronary arteries. The defect, which had been closed completely, was an unusual form of high interventricular septal defect.

Case 9. A. N. After clinical study and cardiac catheterization this 14 month old white female was thought to have an aorticopulmonary fistula. Severe pulmonary hypertension was present with a large pulmonary artery. At 14 months she weighed only 11 pounds. Operation was done on Jan. 11, 1954, under hypothermia. The rectal temperature was reduced from 37 C. to 32 C. in 21 minutes by the use of an ice bath. After removal the tem-

perature further decreased to 25.5 C. At operation a large patent ductus arteriosus was found, divided and closed. Cardiac rhythm was normal except for occasional extra systoles. At the conclusion of the operation the child's temperature was 27 C. She was placed in a water bath at 42 C. and in 30 minutes the temperature had reached 35 C. Her course since operation has been one of steady improvement.

Case 10. J. W. This 5 month old male infant had had a brassy wheezing cough, stridor, cyanosis and repeated respiratory infections since birth. The pre-operative diagnosis was tetralogy of Fallot with right aortic arch and vascular ring compressing trachea and esophagus. On Feb. 27, 1954, operation was done under hypothermia. After 22 minutes in the ice water bath the temperature had fallen to 31 C. Following removal, the temperature dropped further to 27 C. At operation the vascular ring (vestigial left aortic arch) was divided and an end to side anastomosis was made between left subclavian and left pulmonary arteries. The infant tolerated the procedure well. After operation he was placed in a water bath at 42 C. and in 30 minutes the temperature had risen to 35 C. The infant's color was improved by operation and stridor was alleviated. However, excessive tracheobronchial secretions necessitated tracheostomy 24 hours after operation. The infant's course was a stormy one with several episodes of severe respiratory distress and peripheral collapse. Patchy tender areas of subcutaneous fat necrosis appeared about one week after operation. On the ninth postoperative day there was a sudden spurt of a small quantity of blood from the tracheostomy tube followed by apnea, peripheral collapse and death. Autopsy revealed erosion of the tracheal wall with granulations above the carina and in the orifice of the left main bronchus. The left lung was atelectatic. Examination of the heart showed a patent subclavian-pulmonary anastomosis; there was a right aortic arch, right descending aorta and a single ventricle with severe stenosis of the pulmonary orifice. Subcutaneous fat showed nodular areas of fat necrosis.

Case 11. W. F. S. This undersized 3 year old girl had been cyanotic and short of breath since the age of 6 months. On physical examination a harsh systolic murmur and thrill was found along the left sternal border. The electrocardiogram, chest roentgenogram, and fluoroscopy were all within normal limits. Cardiac catheterization revealed severe pulmonary stenosis, probably *pure* pulmonic stenosis with right ventricular hypertension. On March 24, 1954, the patient's temperature was reduced from 37 C. to 32 C. by placing her in a bath of ice and water for eight minutes. Bilateral anterior thoractomy was carried out and inflow stasis produced. The pulmonary artery was opened and the pulmonic valve inspected. This inspection revealed a nonstenotic bicuspid valve below which was a high infundibular diaphragm. Following closure of the artery and release of the inflow stasis, which had been of three minutes duration, the patient was again hyperventilated. Once again the cavae were occluded and one minute later a clamp was placed across the outflow tracts so as to occlude the coronary arteries. Through a right ventricular incision an infundibulectomy and suture closure of a small high interventricular septal defect were performed. The duration of inflow and outflow stasis had been of 8½ minutes and 6¾ minutes respectively. The heart maintained good color; contractions were at first weak but soon improved. The only electrocardiographic changes were occasional premature ventricular contraction and transient S-T segment depression. After closure of the chest, the patient's temperature was raised from 27 C. to 36 C. by placing her in a bath of hot water at 40 C. for 27 minutes. Her color was immediately improved and her postoperative course uneventful.

DISCUSSION

The importance of hyperventilation during hypothermia, as stressed by Swan and his associates,[25] is confirmed by the experimental part of this study. Ventricular fibrillation is the most common cause of death in animals which fail to survive operative procedures under hypothermia. This is true whether cardiac venous inflow stasis is produced or not. Once ventricular fibrillation has occurred under conditions of hypothermia it is exceedingly difficult to revert it by the usual

methods. Brown and Miller[10] and Miller and associates[19] have shown that sudden extreme changes in CO_2 levels play an important role in the development of ventricular fibrillation. It has been demonstrated by others that myocardial hypoxia alone is not responsible for the phenomenon.[16, 20] Swan and his associates have utilized these observations to render dogs hypocapnic by overventilation during cooling in order to prevent excessively high CO_2 buildup and to attempt to produce deliberate respiratory alkalosis. By this means they reduced the incidence of ventricular fibrillation in their experiments to about 8 per cent. Whether the reduction in the stimulus to fibrillation by hyperventilation can be attributed to control of serum CO_2 levels or to prevention of a fall in pH remains unsettled. We have insufficient evidence in this regard to permit comment, but the data summarized in table I amply confirm the over-all conclusion that hyperventilation substantially reduces the incidence of ventricular fibrillation in hypothermic dogs.

Another phase of the experimental part of this study from which a rather definite conclusion may be drawn is that concerning outflow tract occlusion. Outflow stasis by means of a noncrushing clamp applied to the base of the pulmonary artery and aorta so as to occlude the orifices of the coronary arteries has been advocated by Lewis and Taufic[18] as a means of preventing air embolism during open heart surgery under hypothermia involving the left auricle or ventricle. Swan[24] has shown by perfusion experiments that coronary artery flow is effectively interrupted by this method and both he and Lewis and Taufic have been able to prevent coronary air embolism experimentally and clinically by this maneuver. The present experiments with inflow and outflow stasis do not dispute the value of outflow tract occlusion as a means of preventing air embolism but they do show that the combination of inflow and outflow stasis is tolerated well by the hypothermic dog's heart for only five or six minutes. The data in table II indicate that the combination of inflow and outflow stasis is much more hazardous for a 10 minute period than is inflow stasis alone. It may be that some coronary artery flow, regardless of how small, persists with inflow stasis alone and prolongs myocardial tolerance beyond the period which is tolerated with total interruption of coronary arterial perfusion. This observation is in keeping with Cohen's demonstration[11] that the very small venous return to the heart carried by the azygos vein extends survival beyond that possible with total interruption of venous return.

The immersion method for production of hypothermia has proved to be quite satisfactory in our limited clinical experience. After a short while, the operating team and anesthesiology group become very proficient in the use of the method and very little extra bother or confusion is produced in the operating room. In infants and young children only 12 to 30 minutes in the ice water has been required to reduce body temperature to the desired range. In each child a further drop of about 5 C. has occurred after removal from the cold bath. In the 1 adult, in whom the immersion technic has been used, 48 minutes were required to reduce the temperature to 30 C. with a further drop to 28 C. after removal from the ice water. Similarly, we have found no great disadvantages in the use of immersion in warm water as a means of rewarming after operations under hypo-

thermia. By removal from the warm bath when body temperature has risen to 35 C. no *rebound* hyperpyrexia has been encountered in any patient.

Although to date we have used hypothermia in only a small number of poor-risk patients who have had cardiac surgery, it is our present opinion that the reduction of body temperature has been of definite value. In cyanotic infants under 2 years of age with congenital pulmonary stenosis the operative mortality rate without hypothermia has ranged around 30 to 35 per cent.[4] Many of the deaths have occurred from cardiac arrest during operation. In the 7 cyanotic infants of the present study cyanosis disappeared during hypothermia, as it frequently does in the less severe cases with the basal conditions of anesthesia and an oxygen-rich anesthetic mixture. However, in several instances in which anastomosis was done, the venous blood in the pulmonary artery was of a well oxygenated, bright red color. The myocardium remained pink throughout each procedure and in no instance did cardiac arrest or ventricular fibrillation occur. In the single cyanotic adult in whom the technic has been used, the value of hypothermia was less convincing as intense cyanosis persisted despite the lowered temperature. However, this extremely ill patient who had had a previously unsuccessful infundibulectomy for tetralogy of Fallot and who had persistent auricular flutter at the time of her second procedure withstood well a subclavian-pulmonary anastomosis under hypothermia and during the rewarming phase reverted to a sinus rhythm.

In the 2 patients thought preoperatively to have congenital aorticopulmonary fistula hypothermia was used in an effort to reduce the tendency to cardiac arrest during the closure of the fistula by the division and suture method.[23] In addition, it was believed that the reduction in arterial pressure, cardiac output and heart rate under hypothermia would facilitate the technical maneuvers necessary for the closure. In each instance, at operation, a patent ductus arteriosus was found, with successful division in 1 patient. The development of acute cor pulmonale and cardiac arrest in the other patient after division of his huge ductus, we believe, can be attributed to extreme pulmonary hypertension with reversal of the ductal flow and we think that this phenomenon was not related to hypothermia.

In 2 patients stasis cardiotomies were done for intracardiac procedures under direct vision, with one death from ventricular fibrillation and one success. The fatal ventricular fibrillation occurred during the closure of an unusual form of high interventricular septal defect which functioned as a shunt between left ventricle and right atrium. At least two preventable errors were made, both of which are fibrillatory stimuli. One was to use cardiac inflow and outflow stasis for too long a period (11 and 10 minutes respectively) while identification, evaluation and suture of the unusual defect were accomplished. The second error in this case was to permit air to be trapped in the left ventricle when the defect was closed and coronary air embolism resulted. In the other patient, a 3 year old girl with tetralogy of Fallot and right ventricular hypertension, stasis cardiotomy under hypothermia permitted excision of the infundibular diaphragm and closure of the interventricular septal defect under direct vision with an immediate result which seems to be excellent.

The only postoperative complication encountered in this small group of patients which can be directly attributed to hypothermia is subcutaneous fat necrosis. No instances of frostbite have occurred. Subcutaneous fat necrosis of a patchy, clinically apparent variety with characteristic histologic changes developed after hypothermia in 2 young infants (cases 1 and 10), 4½ and 5 months of age; it probably accounted for the *knots under the skin* observed by the parents and family physician in an 18 month old baby (case 3) after discharge from the hospital following operation under hypothermia. This phenomenon, which is apparently the result of cooling to the point of solidification of subcutaneous fat having a high melting point as is found in young infants, has been discussed recently by Stahlman and two of us.[12] Experiments concerning the production of fat necrosis by hypothermia with relation to dietary fats are to be reported soon from this laboratory.[1] At present, we believe that subcutaneous fat necrosis of the type which we have observed after hypothermia is not a serious complication.

On the bases of these experimental and clinical observations it is our opinion that hypothermia offers advantages in cardiovascular surgery which warrant its continued and more extensive use. It should be emphasized that thus far we have used cooling only in patients considered to be extremely poor surgical risks. We have *leaned over backwards* in this respect so as not to let our interest in hypothermia allow its use as a panacea. All older children and adults with congenital cyanotic heart disease (with a single exception) during the period of this study have been submitted to operation without hypothermia. In two instances fatal cardiac arrest has occurred in these *average* or *good-risk* patients. As a result of this experience we plan to extend the indications for hypothermia to include its use in all patients with congenital heart disease in whom a serious danger of myocardial anoxia is anticipated during operation. Despite the strict limitations of time, the opportunity afforded by hypothermia and stasis cardiotomy to carry out corrective intracardiac procedures under direct vision is most intriguing. It is our plan for the future to use a direct visual approach for congenital heart lesions whenever feasible.

SUMMARY

Experience with hypothermia as an adjuvant in cardiovascular surgery has been described. The value of hyperventilation in the prevention of fatal ventricular fibrillation during operation under hypothermia has been confirmed in experimental studies. A discrepancy in the tolerance to cardiac inflow stasis and outflow stasis in hypothermic dogs has been observed. Eleven patients with severe manifestations of congenital heart disease have been subjected to operation under hypothermia. These experimental and clinical observations indicate that hypothermia offers advantages in cardiovascular surgery which warrant its continued and more extensive use.

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HEPARIN REBOUND

A CLINICAL AND EXPERIMENTAL STUDY

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The term *heparin rebound* refers to a postulated period of hypercoagulability of the blood following prolonged hyperheparinemia. Such a mechanism has been proposed to explain, at least in part, recurrences of phlebothrombosis and/or pulmonary embolism following the abrupt cessation of heparin therapy.[1-4, 6] Other factors which may be of importance in such recurrences are: (1) clinically undetectable residual disease secondary to heparinization, inadequate either in dosage or longevity of treatment and (2) continued venous stasis associated with the nonambulatory patient.

We have been impressed by the rapidity of reappearance of symptoms in some of our patients who had been treated with Depoheparin and ambulated for at least 48 hours prior to its discontinuance. Three illustrative cases are reported. We have believed also that rebound hypercoagulability might be of significance in such instances. We are not aware of any previous investigations designed to test the presence or absence of a heparin rebound phenomenon in the experimental animal. Five such experiments are recorded. When subjected to statistical analysis they appear to confirm the presence of a transient state of hypercoagulability following prolonged artificially induced hyperheparinemia.

LABORATORY EXPERIMENTS

The subjects of the experiments were 5 mongrel dogs selected at random. They were individually caged and fed a standard ration throughout the testing period.

A three tube heparin sensitized clotting time as employed by de Takats[5] and modified from the one tube test described by Rosenthal[10] was selected. A few minutes prior to venipuncture 0.1 cc. of a sólution of saline containing 4 micrograms of crystalline sodium heparin was placed in each of three clean, dry Pyrex test tubes, 13 by 100 millimeter, and allowed to contact the lower third of the tubes by tilting and rotation. The tubes then were placed in a rack. The dogs were prepared by securing them to a trough table and shaving and preparing the inguinofemoral regions with 70 per cent alcohol. Ten cc. of blood was withdrawn from a femoral vein with a 19 gauge needle and a 10 cc. clean, dry glass syringe. Only samples resulting from a clean penetration of the vein wall and unhampered flow of blood were utilized. One and one-half cc. of blood was placed as gently as

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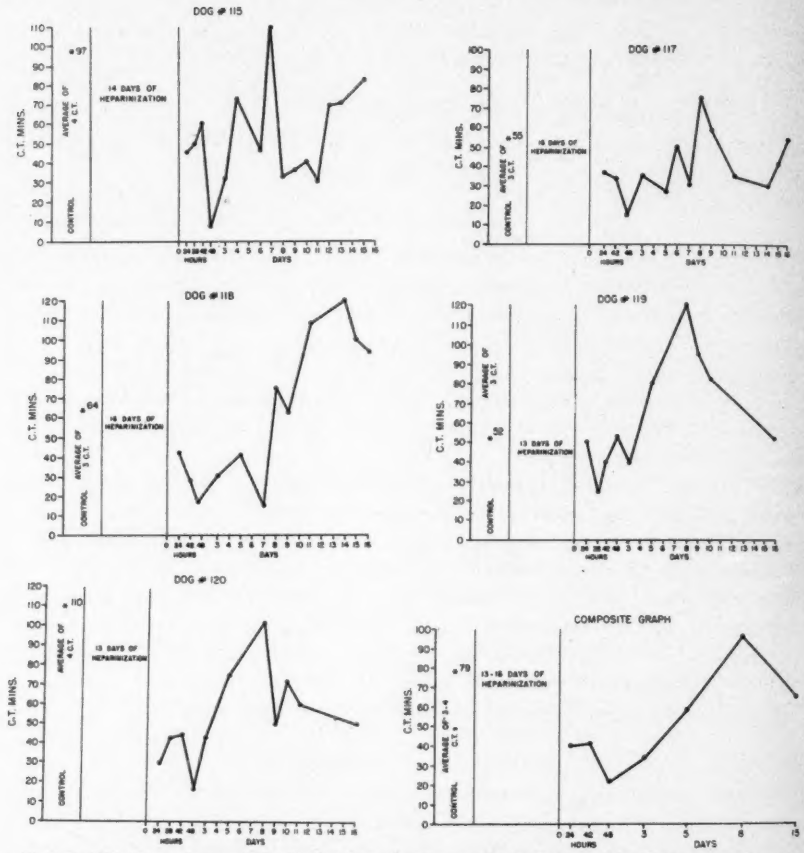

FIG. 1. The heparin-sensitized clotting times are charted for each of the experiments described in the text with a composite graph in the right lower corner.

possible into each of three tubes labeled No. 3, No. 2 and No. 1 in that order. The remaining blood was discarded. Admixture of the heparin solution with the blood was increased by tilting the tubes one time. Tube No. 1 was then examined by tilting every five minutes until the red cell mass ceased to flow. This was taken as the end point. Subsequently, tubes No. 2 and No. 3 were examined and the final reading taken from tube No. 3. This reading was identical with that described by McCleery and associates[9] in their work with silicon clotting times.

Either three or four control sensitized clotting times were made on each dog, usually on successive days. The control values noted in the graphs in figure 1 are the averages of these determinations. Heparinization with Depoheparin* then was begun, utilizing 100 milligrams injected into the deep subcutaneous tissues

* The heparin used in these experiments was supplied by The Upjohn Company of Kalamazoo, Michigan.

of the shoulder or buttocks every 24 hours. Spot checks of the clotting times by the Lee-White method attested to the adequacy of heparinization in each experiment. As noted in the graphs, heparinization was continued 14 days in one experiment, 13 days in two and 16 days in the remaining two. Twenty-four hours after the final injection of Depoheparin a heparin sensitized clotting time was made and subsequently at 28, 42 and 48 hours and daily thereafter until the experiment was terminated. The study was begun initially with dog No. 115. After a week, dogs No. 117 and No. 118 were included and finally a week later dogs No. 119 and No. 120. Aside from small hematomas no adverse effects were noted either as a result of the heparin injections or the repeated obtaining of blood samples.

RESULTS

The control heparin sensitized clotting times ranged from 40 to 137 minutes with an average of 73 minutes (fig. 1). Others (McCleery and associates[9]) who have worked with the highly sensitized silicon tube clotting time have had a similar experience. It probably is true that there is a valid variation of wide range with so sensitive a test. The heparin sensitized clotting times 24 hours after the last injection of Depoheparin averaged 41 minutes—32 minutes less than the average of the controls. Although this appears to be significant, variation of the control values prohibits a statistically valid statement. The same is true of the 28 hour and 42 hour clotting times.*

The most significant drop in clotting times occurred at 48 hours following the last injection of heparin. In 4 of the 5 animals (115, 117, 118, 120) this value was extremely low. In the remaining experiment (119) the 48 hour clotting time was equal to the average of the control values and the low point was reached at 28 hours. According to the method of analysis of variance the shortening of the 48 hour clotting times is highly significant ($p \ll .001$) when compared with the preheparinization control values. There subsequently was a gradual but irregular rise in clotting time so that by the sixth to eighth day the values attained the control levels and in 4 of the 5 animals overshot the control values. Thereafter, the clotting time tended to return to normal. It would appear that there is a secondary period of hypocoagulability between the sixth and eighth postheparin days. This observation cannot be substantiated statistically from the data at hand.

CASE REPORTS

Case 1. J. G. L. was admitted to the hospital on May 15, 1951 and was discharged on June 14, 1951. This 43 year old white man was admitted to the Vanderbilt University Hospital for the second time complaining of pain in the right hemi-thorax and shortness of breath. Previous admission was on April 3, 1951, at which time a craniotomy was done for removal of a chromophobe adenoma. He was discharged from the hospital on April 17, 1951 after a relatively uneventful postoperative course. In retrospect it was recalled that he had noted slight discomfort in his left calf just prior to discharge from the hospital.

Following discharge his left calf gradually became more tender, associated with progres-

* Data analyzed by Mr. Edwin Bridgeforth, Instructor in Biostatistics in Preventive Medicine and Public Health.

sive swelling of that extremity. Three days prior to admission he suddenly became short of breath and noted *tightness* in his chest. The day prior to admission he experienced the sudden onset of an unremitting pain in the right hemi-thorax with an increase in dyspnea.

On admission to the hospital he was markedly dyspneic. A friction rub was present over the right lower lung field. The left calf was slightly larger than the right. However, there was no tenderness or pitting edema and Homans' sign was negative. Roentgenographic examination of the chest revealed findings compatible with a pulmonary infarction. Depoheparin therapy was begun immediately, 200 mg. every 20 to 24 hours. The Lee-White clotting times were maintained at a level higher than 25 minutes for 14 days. Treatment was stopped abruptly at that time. The patient had been ambulatory for 48 hours. There were no residual signs or symptoms of phlebothrombosis. The right lung had cleared considerably, both by physical examination and roentgenographically.

Forty-eight hours after the last injection of heparin swelling, pain, and tenderness again developed in the left calf. Depoheparinization was restarted. Three hundred mg. every 20 to 24 hours was required to maintain a clotting time above 25 minutes. Therapy was continued for six days and again discontinued abruptly. No further acute episodes or pulmonary complications occurred. However, dependent edema of the left leg still was present a little over two months after discharge.

COMMENT

The recurrence of local symptoms corresponded well with the period of maximum hypercoagulability of the blood noted in the laboratory experiments. The lack of clinically detectable phlebothrombosis at the time of discontinuance of heparin therapy however, does not rule out the presence of residual disease. The increased dosage of heparin required to produce the same elevation in clotting time with the second course of therapy as compared to the first would indicate an increase in heparin tolerance. Although the second course of therapy was short and again abruptly discontinued, there was no recurrence of acute symptoms.

Case 2. N. M. N. was admitted to the hospital on May 26, 1952 and was discharged on June 25, 1952. This 42 year old Negro woman first was admitted to the Vanderbilt University Hospital complaining of pain in the left side of the chest. Ten days prior to admission she fell and sprained her left ankle. Eight days prior to admission she developed swelling, pain, and tenderness in her left calf. Three days prior to admission she was seen in the Outpatient Department and treated at home with penicillin and bed rest with elevation of the extremity.

Two hours prior to admission she experienced the sudden onset of severe pain in the left hemi-thorax, followed by difficulty in breathing. The impression that she had had a pulmonary embolus was substantiated by hemoptysis the following day and by roentgenographic examination of the chest.

Depoheparin therapy, 300 mg. every 24 hours was begun on admission to the hospital and continued for nine days. On the tenth and eleventh days, 200 mg. were administered. Prior to discontinuation of therapy on the eleventh day the patient had been ambulatory for 48 hours and was symptom free.

Seventy-two hours after the last heparin injection pain, tenderness and swelling in the left leg recurred. Depoheparin again was started—300 mg. being administered daily for two days. Dicumarol was given simultaneously and was continued on an ambulatory basis for one month. The acute symptoms subsided promptly. No further acute episodes were experienced but there was persistent edema of the left leg two months after discharge.

COMMENT

This case is similar in most respects to the previous one. The recurrence of local disease again corresponds with the period of hypercoagulability noted in the laboratory experiments. Initial treatment was delayed and persistent edema resulted. The prolonged period

of therapy with dicumarol on an ambulatory basis was instituted with the idea that it would most satisfactorily allow the mechanisms involved in the heparin rebound phenomenon to stabilize and any residual thrombotic processes to subside.

Case 3. M. Y. was admitted to the hospital on March 20, 1952 and was discharged on May 15, 1952. This 66 year old white woman was admitted to the Vanderbilt University Hospital because of an exsanguinating hemorrhage from a duodenal ulcer. A subtotal gastrectomy was done on the day of admission. The postoperative course was uncomplicated until the tenth postoperative day. At that time the patient noted the sudden onset of pain in the left chest. She previously had been ambulatory with no symptoms or signs of phlebothrombosis. Roentgenographic examination of the chest revealed a shadow in the left lower lung field compatible with a pulmonary infarct. Depoheparin therapy in doses of 200 mg. every 20 to 24 hours was begun immediately, producing therapeutic elevation of the clotting time (25 minutes or above by the Lee-White method). On the day following the first dose of heparin, tenderness and consistency changes in the left calf were noted. Heparin therapy was continued for 10 days, at which time the patient was ambulatory and asymptomatic.

Approximately 36 hours after the abrupt cessation of heparin another pulmonary embolism occurred and heparin therapy was again started in the same dosage as previously. Two days later there were symptoms and signs of another small embolus. The quantity of Depoheparin administered was increased to 300 mg. every 20 to 24 hours. This schedule was continued for nine days, at which time the dose was decreased to 200 mg. and dicumarol was started simultaneously. Dicumarol therapy was continued on an ambulatory basis for approximately one month. There were no further symptoms of thrombo-embolism There has been no noticeable edema of the involved extremity.

COMMENT

Again the recurrence of symptoms corresponds well with the period of hypercoagulability noted experimentally. In contrast to the 2 previous cases the manifestation of recurrence was in the form of pulmonary embolism. As with the first case, increased quantities of Depoheparin were necessary in order to produce the desired elevation of clotting times during the second course of heparin therapy. Dicumarol therapy on an ambulatory basis was continued for a prolonged period. Treatment was begun early and there have been no residual symptoms of the local process.

DISCUSSION

Heparin has been widely used in the treatment of thrombo-embolism because of the relative ease with which its anti-coagulant effect may be controlled. Among the complications of such treatment which have been of concern are occasional recurrences of symptoms either locally or in the form of pulmonary embolism or both. The etiologic factors which have been suggested to explain such recurrences are: (1) clinically undetectable residual disease secondary to inadequate heparinization either in dosage or longevity of treatment. (2) Continued venous stasis associated with a nonambulatory patient, and (3) a postulated period of hypercoagulability of the blood of a rebound nature following the abrupt cessation of heparin.[1-4, 6] We have applied the term *heparin rebound* to this phenomenon.

Crafoord[3] recorded several cases in which pulmonary embolism occurred following the discontinuation of heparin therapy. He recommended that the heparin treatment be continued as long as possible and that the dose be gradually decreased prior to discontinuation. De Takats[4] has stated that such recurrences were due primarily to the early discontinuation of heparin therapy. He stated that he thought, however, that a rebound period of hypercoagulability might be

of some significance. Vander Veer[11] and Cadenhead[2] reported single instances of recurrent pulmonary emboli following abrupt withdrawal of heparin therapy. Loewe[6] stated that "occasionally patients who are on heparin therapy may—following an abrupt withdrawal of the drug—develop a di-phasic phenomenon wherein the blood becomes hypercoagulable. This phenomenon is obviated by a gradual decrease of the repository heparin therapy." Artz[1] has recorded 2 cases of fatal pulmonary embolism following the abrupt cessation of repository heparin therapy. In 1 of the patients the treatment was considered prophylactic. He, too, indicated that he believed that the blood is hypercoagulable for 1 to 2 days following such therapy.

On the basis of his studies with heparin utilized in the treatment of experimental venous thrombi in rabbits, Loewe[7] believes that repository heparin therapy should be continued for at least 14 days. The initial course of heparin therapy in the 3 cases reported in this communication was 14 days in case 1, 11 days in case 2 and 10 days in case 3. All 3 of the patients were ambulatory and symptom free at the time the drug was discontinued.

Depoheparin therapy has been administered to all of our patients according to the plan outlined by McCleery and associates.[8] The initial dose of Depoheparin is determined by the results of a heparin tolerance test. Any subsequent changes in the amounts or frequency of administration are controlled by the repeated determinations of coagulation time by the Lee-White method.

The results of the five experiments reported are depicted in figure 1. Depoheparin was administered to mongrel dogs for a period varying from 13 to 16 days. According to the method of analysis of variance a highly significant ($p \ll .001$) lowering of the heparin sensitized clotting times occurred at 48 hours following the abrupt discontinuation of heparin. The heparin sensitized clotting time had returned to normal or above by the sixth to eighth postheparin day.

We have taken these data to indicate that, in the dog at least, a heparin rebound phenomenon does occur.

The relative importance of the various etiologic factors which have been suggested would be difficult to assess in a given case of recurrent thrombo-embolism. Heparin therapy probably was discontinued too early in 2 of the patients whose cases are reported. It appears obvious that a combination of residual thrombosis with a period of hypercoagulability would be more detrimental than either factor alone.

Two alternative methods of obviating the heparin rebound phenomenon immediately suggest themselves: (1) the gradual discontinuation of heparin therapy[1, 3, 4, 6] (2) a switch to therapy with prothrombin depressants. We have not had sufficient experience to offer an opinion as to which of these two methods is the better. We have chosen a switch to dicumarol therapy on an ambulatory basis because of its greater ease of administration and the earlier discharge of the patient from the hospital. Reasoning on an entirely theoretical basis, we believe further that this method would allow the mechanisms involved in the heparin rebound phenomenon to readjust in an unimpeded manner. The dose of dicumarol has been adjusted prior to discharge of the patient to a level at which it was thought that treatment on an outpatient basis was entirely safe.

SUMMARY

In addition to other factors, it has been suggested that a rebound period of hypercoagulability of the blood following prolonged artificially induced hyperheparinemia might be of importance in recurrences of thrombo-embolism. The term *heparin rebound* has been applied to this phenomenon.

Five laboratory experiments utilizing mongrel dogs were made in order to test this hypothesis. A statistically significant lowering of the heparin sensitized clotting time occurred at 48 hours after the discontinuation of repository heparin administered for an average of two weeks. Methods of avoiding the heparin rebound phenomenon have been suggested. Three illustrative cases have been recorded.

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THE ESTABLISHMENT OF AN ARTERIAL BANK USING LYOPHILIZATION AND ETHYLENE OXIDE STERILIZATION

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Carrel,[3] in the first part of this century, demonstrated the feasibility of homologous vascular transplantation. Clinical application to a significant extent has come only in recent years. The series of cases reported by Gross,[8] Bahnson,[1] DeBakey and Cooley,[4] Hufnagel,[10] Brown,[2] and others have amply demonstrated the clinical practicability of arterial homotransplantation.

While extirpation of the diseased part and restoration of normal function by interpolation of a suitable graft has become the preferred treatment in many instances, this procedure presupposes that such grafts are available. The availability of suitable homologous arterial segments is assured by the existence of a *vascular bank*. In order to establish a *bank* an adequate method of preservation and storage must be devised. Such methods have been the subject of vast experimentation since the time of Carrel. Gross and his associates[9] have been successful in the preservation of vessels for a limited period of time in nutrient media. The efficacy of this method is attested by Gross'[8] recent statement that such grafts have been used successfully in 42 patients with coarctation of the aorta. Rigid temperature and bacteriologic controls and a six week storage time limit are its major disadvantages. The tissue culture viability of the graft is maintained by this method for a period of six weeks—a questionable advantage.

Lyophilization or the freeze-drying method of preservation and storage of vessels was introduced by Marrangoni and Cecchini.[14] This entails rapid freezing of the vessels at a very low temperature and sublimation of the water by subjecting the vessel to a high vacuum. When dehydration is complete, the vessels are sealed in vacuum tubes and stored at room temperature. The rapid freezing prevents large ice crystal formation with consequent structural defects and the sublimation dehydrates the vessels without shifts in the intracellular and extracellular diffusible constituents. Sterile vacuum storage prevents oxidation of residual lipids and decomposition. Such vessels have been used successfully after more than two years' storage. The antigenicity of freeze-dried vessels seems to be insignificant.

After lyophilization, tissue culture viability is not present. That viability may be harmful is indicated by the work of Pate and Sawyer.[17] Fresh grafts display an electric potential difference; freeze-dried grafts have none. "The potential difference of fresh grafts is abnormal in that the usual negatively charged intima, with respect to the adventitia and blood stream, becomes positive and attracts

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negatively charged platelets predisposing the vessel to thrombosis."[17] The lack of an injury potential in lyophilized grafts may explain the almost complete absence of even microscopic thrombosis in these grafts.

Although lyophilized vessels do not retain tissue culture viability, the necessary functional integrity is maintained. The major function of a large artery is to serve as a conduit. Freeze-dried grafts are capable of doing this until replaced by host tissue. Endothelialization occurs rapidly, followed by ingrowth of fibrous tissue. Freeze-dried grafts have been used in a vast number of experimental animals with excellent results over long periods of time.[16] Successful clinical use is the subject of several reports in the current literature.[1, 2, 10] Long term clinical results must await the passage of time.

The procurement of vessels from otherwise suitable donors is sharply curtailed by the lack of an adequate sterilization process. Infectious disease, bacteremia, contamination in operative fields, and the lack of ready accessibility to suitable donors in other hospitals result in the loss of a considerable number of vessels.

Several methods of sterilization of arterial segments have been tried; cathode ray irradiation[15] and various antiseptic solutions[10] being the most notable. These have proved unsatisfactory in general because of the deleterious effects upon the vessels. The sterilizing properties of ethylene oxide have been extensively investigated.[12, 19] Hufnagel recently has used this organic gas for the sterilization of arterial grafts.[10] Sterilization seems to be reliable by this method. Either the liquid or gaseous form of ethylene oxide may be used. The former seems to be the more easily handled, and the exposure time for effective sterilization is considerably shortened.

In the past year we have established an arterial bank at the Vanderbilt University Hospital using ethylene oxide sterilization and the lyophilization method of preservation. The bactericidal and histotoxic effects of ethylene oxide as a sterilizing agent have been assessed in animal experimentation. Lyophilization, as a method of preservation, is being evaluated by histologic studies and animal homotransplantation.

CRITERIA FOR SELECTION OF VESSELS

The rather arbitrary criteria for obtaining vessels are that the donor be between the ages of 5 and 60 years and that the interval between death and necropsy be less than eight hours. These age criteria are less stringent than those proposed by others.[6] There is only fair correlation between age and the degree of aortic sclerosis.[6] A vessel free of sclerotic changed probably can fulfill its function as a blood conduit regardless of age.

It usually is possible and certainly desirable to obtain vessels within eight hours after death. However, the time interval between death and refrigeration undoubtedly is the more critical element.[6] Actually grafts obtained from 16 to 35 hours after death have been used clinically.[6]

Since the institution of the ethylene oxide method of sterilization, bacterial infection has not been a deterrent to the acquisition of vessels. If positive cultures

occur following sterilization with ethylene oxide, the vessels are discarded. In our experience to date, there have been no positive cultures from vascular segments following sterilization by this method.

The use of vascular segments from individuals dying of malignancy is problematic. The lyophilization process renders all cells nonviable.[17] It seems highly unlikely that homotransplantation of nonviable malignant cells would result in the growth of the malignancy, especially when one considers the scant success achieved in transplanting tissue culture viable malignant cells. We have obtained aortic segments from those dying of malignancy but have not implanted them. Vascular segments with malignant invasion are discarded as being structurally unsound. The same applies for segments involved by vasculitis, whether it be of syphilitic or other origin.

PREPARATION OF VESSELS

Sterile technic is not observed. The entire aorta is removed in continuity from the arch to and including as much of the iliac vessels as is possible. The branches are divided 1 cm. from the aorta and are not ligated. The aorta is washed in saline; divided into the desired segments, and stripped of perivascular tissue. Two thoracic segments, a single abdominal segment or "Y" graft, and two external iliac segments have proved to be convenient subdivisions. Any segment demonstrating gross pathologic change is discarded. A small segment of vessel is used for culture and microscopic examination. The segments then are ready for sterilization.

STERILIZATION OF VESSELS

The segments are placed in individual Pyrex test tubes, 25 by 200 mm., with no more distortion than necessary. Sufficient liquid ethylene oxide* to cover the vessel segment is poured into the tubes. After 30 minutes the residual ethylene oxide is decanted. Extreme caution must be used in handling ethylene oxide as it is highly inflammable and explosive, having a boiling point of 10.8 C. The segment for culture and microscopic section is transferred aseptically to a sterile tube of saline solution. This saline solution is cultured for aerobic and anaerobic bacteria and fungi. The segment is then submitted for microscopic examination. With aseptic technic the remaining tubes are stoppered with sterile evacuation assemblies as seen in figure 1. This evacuation assembly consists of a number 5 rubber stopper through which a short length of Pyrex glass tubing, with an internal diameter of 5 mm., is inserted.

The reliability of ethylene oxide as a sterilizing agent has been assessed[20] and confirms the work of Hufnagel.[10] In a series of 15 animals the aortas were exposed to fecal and room contamination. Following treatment with ethylene oxide, as outlined above, cultures for bacteria and fungi showed no growth. Further cul-

* Obtained in 100 Gm. ampules from Distillation Products Industries Division of Eastman Kodak, Rochester 2, New York.

tures, after lyophilization and storage for varying periods of time, yielded no growth. Eight human aortas have been sterilized in a similar fashion, and cultures have shown no micro-organisms.

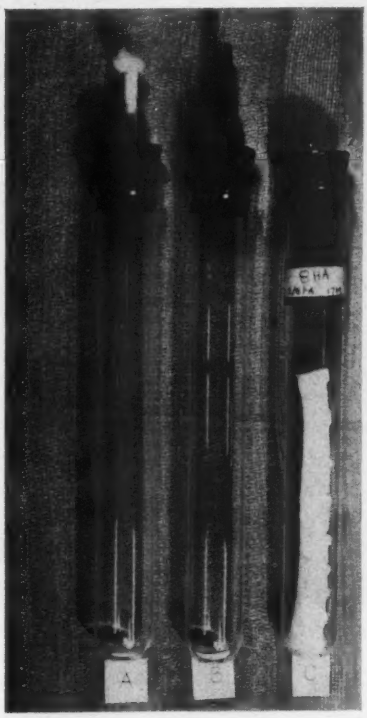

FIG. 1. A. Tube with stopper in place for producing primary vacuum. B. Tube with stopper for producing secondary vacuum and sealing. C. Freeze-dried graft in sealed tube, as stored.

LYOPHILIZATION OF VESSELS

The tubes containing the vascular segments are immersed for five minutes in a bath of 95 per cent alcohol and crushed dry ice (−76 C.). After removal from the bath, the tubes are packed in dry ice until the time of lyophilization. They may be stored in this manner for several weeks.

The lyophilization apparatus consists of a Stokes Cryochem apparatus (model no. 102) attached to a Welch Duo-Seal Pump (model no. 1405H) (fig. 2). This unit is capable of producing a vacuum approximating 0.05 micron. The tubes are attached to the manifold and remain in dry ice for the first 12 hours of the process to preclude formation of macro-crystals of ice. Drying is considered adequate at the end of 36 hours. With aseptic technic the tubes are sealed under a secondary

FIG. 2. Lyophilization apparatus consisting of vacuum pump, desiccant chamber and manifold.

vacuum with a 20 gauge needle inserted through a plain rubber stopper* (see fig. 1). After removing the needle from the stopper, the stopper is coated with two applications of vinyl acetate. This procedure is necessary in order to prevent the minimal leakage which occurs through rubber. The process of sealing under secondary vacuum was selected after considerable difficulty had been encountered in attempting to seal the Pyrex tubing with a gas-oxygen torch under primary vacuum. The tubes then may be stored at room temperature indefinitely. The vacuum is tested periodically with a spark gap tester, and any tubes having lost vacuum are discarded. This has occurred infrequently. No other maintenance is necessary.

RECONSTITUTION

Prior to use the tube containing the vessel of desired size is immersed in tincture of Zephiran® for 30 minutes. The vessel is then removed from the tube and is

* The needle is quite satisfactory for production of a secondary vacuum, but for the lyophilization process it is essential to use Pyrex tubing having an internal diameter of at least 4 mm.[7]

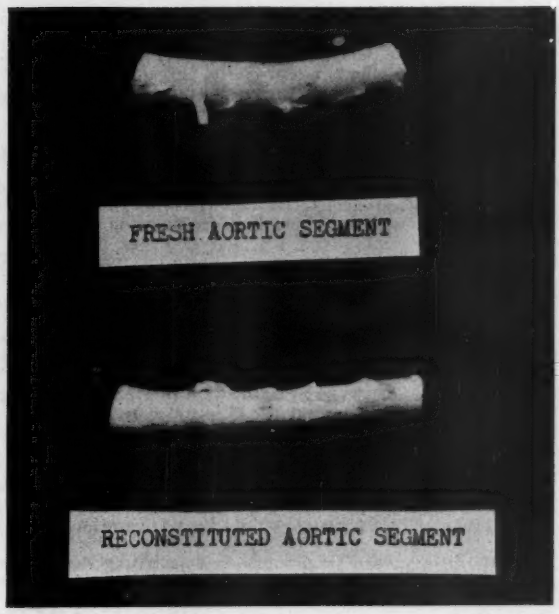

FIG. 3. Comparison between fresh aortic segment and reconstituted freeze-dried aortic segment.

reconstituted by immersion in physiologic sodium chloride solution containing 50 units of penicillin and 50 mg. of streptomycin per milliliter. After 15 minutes the branches are ligated and transfixed with fine silk. The vascular segment then is ready for use. Vessels preserved by this method, after reconstitution, usually resemble fresh grafts in appearance and tensile strength but are slightly less pliable and less elastic (see fig. 3).

SUMMARY

A reliable method for the sterilization and preservation of vascular segments is presented. The criteria for selection of vascular donors are discussed. The technic for preparation and sterilization of vessels with ethylene oxide and preliminary results of sterilization by the method are stated. The process of lyophilization is described.

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MALIGNANT MELANOMA: REVIEW OF SIXTY-THREE PATIENTS

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INTRODUCTION

In order to avoid confusion, the benign melanin-bearing lesions herein are termed *benign pigmented moles* and the malignant ones, *malignant melanomas.* The purpose of this article is to point out the danger of improper treatment of benign pigmented moles and to report the results in the patients with malignant melanomas who have been seen in the Vanderbilt University Hospital from 1925 through 1949.

Although the primary tumor of the malignant melanoma occurs on the skin in about 90 per cent of instances, the recorded five year survival rate is low. The main reasons for such poor results are that many patients do not seek medical advice promptly and that the initial treatment is not carried out properly. The importance of adequate initial treatment has been pointed out by Pack[4] and Gage.[1] Of the patients with malignant melanomas seen in the Ochsner Clinic 80.5 per cent showed recurrences following removal of the primary tumors elsewhere.[1] Pack, Perzik and Scharnagel[5] reported recurrence following operation elsewhere in 64 per cent of their patients.

RELATIVE FREQUENCY

During the quarter of a century covered by this report, 63 patients with malignant melanomas have been observed. Although the average age of patients with such lesions is 49 years, the ages ranged from 20 to 70. Not one child was found to have a malignant melanoma. The sex distribution was equal, the lesion occurring in 32 males and 31 females. Although the ratio of Negro to white admissions was 1 to 9, only 1 malignant melanoma was seen in a Negro.

SYMPTOMS

The duration of symptoms indicates the length of time which the individual had a melanin-bearing tumor (table I), but does not show the length of time that it had been malignant. In only 36 patients (57 per cent) was there a history of a pre-existing benign pigmented mole. Except for the trauma of previous treatment, history of injury or irritation to the benign pigmented mole was recorded in only 10 patients.

We believe that the danger of inadequate treatment should be thoroughly emphasized. Table II shows that 41 patients (66 per cent) had been treated elsewhere before admission. The fact that cauterization or desiccation had been done in 24 per cent indicates that no benign pigmented mole should ever be treated in this manner. It probably is safe to destroy infectious or squamous cell warts by these methods, but one can never be certain that the lesion is a wart and

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TABLE I

Duration of Symptoms before Consulting Physician	Duration of Symptoms before Admission
Average in months	*Average in months*
18.3	31
Range—0 to 120	Range—3 to 156

not a benign pigmented mole, or even a malignant melanoma, until one examines a section of it under a microscope. The defenders of these methods state that cauterization or desiccation does not cause the benign lesion to become malignant, but that the lesion was malignant when first treated. Even if this statement were universally true, it would not justify the method because of the fact that one should determine by microscopic section whether or not the lesion is malignant. If it does prove malignant, proper treatment should be instituted, a procedure impossible to do if the tissue has been destroyed by cautery.

Table II shows that 12 (19 per cent) of the patients had been subjected to simple excision of the lesion before admission; therefore, it could be pointed out that simple excision is almost as dangerous as fulguration. There are two possible dangers of excision. One danger is that of inadequate excision, or cutting through mole cells which might conceivably cause a benign lesion to become malignant. Another danger is that, in excision under local anesthesia, the needle may carry mole cells outside of the limits of the excision. However, even if simple excision were as dangerous as fulguration, after the former procedure tissue is available for study to determine whether or not the lesion was adequately excised and whether or not malignant cells were present. In some instances, after microscopic examination of the excised tissue, the malignant lesions were recognized as such and the patients were admitted for further therapy soon after the excision had been done. The above statements are equally applicable to the use of irritants or chemical cauterization as to the use of fulguration.

The fact that proper initial treatment of a melanin-bearing tumor is increasingly more important is shown in figure 1. Over twice as many benign pigmented

TABLE II

	No.	Per Cent
Treated prior to admission	41	66
Not treated prior to admission	22	34
Types of Treatment Prior to Admission		
1. Cautery or desiccation	15	24
2. Excision, simple	12	19
3. Irritants used by physician	6	10
4. Irritants (home remedies)	3	5
5. Radiation initially	2	3
6. Enucleation	2	3
7. Excision, radical	1	2

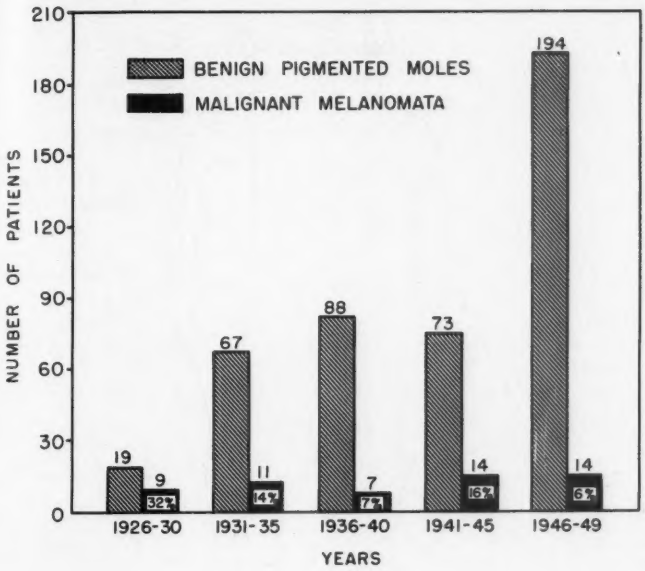


FIG. 1

moles have been excised in the four years from 1946 through 1949 as in any previous five year period. Therefore, since more patients are having moles treated, it has become more and more important that the initial treatment be adequate.

SIGNS

Although practically all of the benign and malignant tumors under discussion show some pigment upon careful microscopic study, some in each category appear clinically nonpigmented. Twenty per cent (table III) of the malignant melanomas of the skin showed no pigment which was detectable on physical examination. If a melanin-bearing tumor is ulcerated, the chances are that it is malignant. Forty-four per cent (table III) of the malignant melanomas of the skin were ulcerated.

SITE

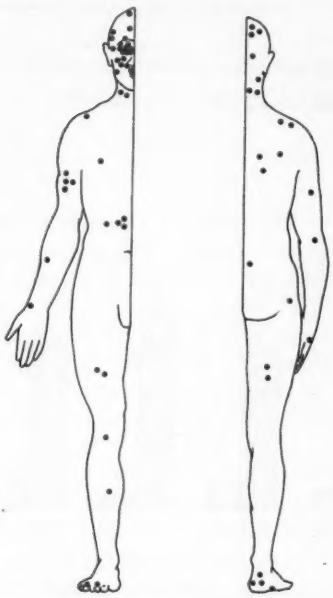
The sites of occurrence are shown in Figure 2. It may be seen that 20 were found on the head and neck in addition to eight tumors of the eye, seven of which

TABLE III

*Characteristics of tumor of skin—55 patients**

	Present		Absent	
	No.	Per Cent	No.	Per Cent
Pigment	44	80	11	20
Ulceration	24	44	31	56

* In 8 additional patients the malignant melanomas were in the eye.



DISTRIBUTION OF 63 MALIGNANT MELANOMATA WHEN DIAGNOSED

FIG. 2

were in the choroid and one on the caruncle. It should be noted (table IV) that only 25 per cent of the tumors were primary, whereas 75 per cent had metastasized when first seen in this clinic.

The clinical diagnosis of malignant melanoma was made in 43 patients (68 per cent), in 39 of whom the tumor was in the skin and in 4 of whom it was in the eye. Erroneous clinical diagnoses were metastatic carcinoma, glaucoma, squamous cell carcinoma, mixed tumor, hemangio-endothelioma, basal cell carcinoma, fibrosarcoma, brain tumor and benign pigmented mole (table V).

The sites of metastases on first admission to the Vanderbilt University Hospital

TABLE IV

Presence or absence of metastases on admission

	No.	Per Cent
Present		
Regional only	27	44
Regional and distant	13	20
Distant only	7	11
Total	47	75
Absent	16	25

TABLE V

Erroneous diagnoses

Diagnosis	No.
Metastatic carcinoma	5
Glaucoma	4
Squamous cell carcinoma	3
Hemangio-endothelioma	2
Mixed tumor	2
Fibrosarcoma	1
Basal cell carcinoma	1
Brain tumor	1
Benign pigmented mole	1
Total	20

TABLE VI

Sites of metastases on admission

	No.	Per Cent
Regional nodes	41	66
Subcutaneous	12	20
Lungs	9	15
Abdominal viscera	7	11
Brain	5	8
Distant nodes	4	6
Bones	2	3

are shown in table VI. These, of course, represent multiple sites in some patients. It is somewhat surprising that bone involvement did not occur more frequently in this tumor, since it metastasizes so early through the blood stream.

TREATMENT

Table VII reveals that 23 (35.5 per cent) patients presented lesions so far advanced that either no operation or only a simple biopsy was done.* In 30 patients (47.5 per cent) the lesions were excised, the excision being so wide in 14 patients that skin grafting was required. In 10 patients, in addition to excision of the primary lesion, regional node dissection was done. *Excision in continuity* with the regional nodes was not done in this hospital from 1925 through 1948.

Although roentgen ray therapy was administered after operation to 20 patients, we have seen no benefit from it and have discontinued its use.

RESULTS

Table VIII shows the outcome in the 63 patients. Obviously, the 2 patients not subjected to operation, and the 21 upon whom biopsy section only was done showed lesions advanced beyond any hope of cure. The average duration of life after admission of the patients who died of tumor was 11.2 months.

* In 2 patients not subjected to biopsy in this clinic, the microscopic diagnosis was established upon examination of tissue removed elsewhere.

TABLE VII

Types of operation

	No.	Per Cent
Biopsy only	21	32.5
Excision, simple	16	25.5
Excision, radical with skin graft	14	22.0
Excision, radical with node dissection*	10	17
None	2	3

* One of these patients had amputation through the thigh and 1 through the leg but none had skin graft.

TABLE VIII

Results

	No.	Per Cent
Living and well five or more years	14*	22
Living and well less than five years	1	2
Dead, result of tumor	44	69
Dead, other cause	3	5
Unknown	1	2

* Two of these died of recurrence six and one-half and eight years after operation.

TABLE IX

Patients without Palpable Lymph Nodes

Sites	No.	Treatment	Survival Time (Yrs.)
Eye	4	Enucleation	5, 8,* 17, 21
Arm	2	Excision and graft	5, 15
Abd. wall	1	Excision and graft	5
Back	1	Excision and graft	5
Neck	1	Excision and node dissection	7†
Cheek	1	Excision and node dissection	7‡
Thigh	1	Excision and node dissection	9‡

Patients with Palpable Lymph Nodes

Shoulder	2	Excision and node dissection	6½,* 9‡
Neck	1	Excision and node dissection	11‡
Total	14		

* Died of malignant melanoma.
† Died of nephritis without recurrence of malignant melanoma.
‡ Microscopic examination of the nodes showed malignant melanoma.

In 40 patients excision with or without skin grafting and with or without regional node dissection was done. Of these patients, 12 are alive and well. Less than five years have elapsed since the treatment of 1 patient (3.5 years). The times of survival of the 12 patients range from 5 to 21 years. Table IX gives the data on the 14 patients who lived more than five years after operation. Of the 8 patients in whom the malignant melanomas were in the eyes, 4 survived the five year period, 1 of them dying of the disease six and one-half years after operation.

Excluding the 1 patient in whom five years have not elapsed since treatment and the 2 who died of malignant melanoma six and eight years after operation, 12 or 20 per cent of the 60 patients were apparently cured. If one considers only the 40 patients in whom the lesion was not too far advanced to permit curative therapy, the 12 patients represent apparent cures in 30 per cent.

COMMENT

As other investigators have suggested, the arbitrary time of five years is not a long enough period, particularly in malignant melanoma, to evaluate results properly. Two of the 14 five year survivors subsequently succumbed to the tumor. It is of interest that a survival rate of 30 per cent occurred in the 40 patients subjected to definitive surgical therapy when none of these patients had the radical *excision in continuity* procedure based on Handley's permeation principle.[2] Five of the 12 patients did have regional node dissection. Four of these 5 patients had microscopic evidence of metastases in the regional nodes excised. Two of these 5 patients had lymph nodes which were palpable before operation—whereas 3 did not. McCune[3] stated that clinical evidence of metastasis to lymph nodes makes the outlook almost hopeless even with radical surgery; whereas, in 7 patients with microscopic, but not clinical, lymph node metastases, 3 or 43 per cent survived five years. During the period 1941–1945 Pack[4] found that the five year survival rate was 14.1 per cent when the nodes showed microscopic evidence of metastasis and 31.8 per cent when they did not.

CONCLUSIONS

Cauterization, desiccation, fulguration or chemical caustics should never be used in the treatment of moles or skin tumors which might be moles.

Five years is not an adequate length of time to indicate that a malignant melanoma is cured, since 2 patients in our series had recurrence six and one-half and eight years, respectively, after operation.

If the initial treatment of a malignant melanoma is adequate, the chance of effecting a five year survival is good, being 30 per cent in our patients.

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ATYPICAL FACIAL NEURALGIA DUE TO TUMORS OF THE GASSERIAN GANGLION

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Of all the clinical syndromes in which pain is a predominant characteristic, tic douloureux in its classical form perhaps is the easiest to recognize. Due to the very typical nature of the painful attacks the diagnosis is seldom mistaken. On the other hand, facial pain of atypical form, frequently is dismissed as a *form* of tic douloureux. A careful evaluation of the character and distribution of the pain and the absence of the usual dolorogenic or *trigger* zone will aid in the differentiation. If, in addition, there is unmistakable involvement of the motor or sensory function of the trigeminal nerve the diagnosis of tic douloureux should be avoided. Impairment of function of any of the cranial nerves in the paratrigeminal area or in the cerebellopontine angle will mitigate against the diagnosis of true tic douloureux. In such instances, the diagnosis of tumor involvement of the fifth cranial nerve becomes highly tenable.

Facial neuralgias of tumor origin were considered by Cushing[3] to be due to the following situations: (1) pressure on the root of the fifth nerve by tumors of the cerebellopontine angle; (2) direct pressure on the ganglion from a tumor located above the ganglion; (3) pressure on the ganglion from below by tumor of the pterygoid fossa or temporal bone; and (4) tumors arising in the ganglion itself. Peet[10] has added two additional situations to complete the classification: involvement of the ganglion by extracranial tumor extending centrally via a peripheral branch of the nerve, and metastatic tumor of the ganglion.

An appreciation of the clinical features of atypical facial neuralgia combined with an understanding of the pathologic situations outlined above will permit an intelligent search for neoplastic disease as the offending agent and may obviate the ineffective and inefficient minor procedures on the peripheral branches in an attempt to relieve pain.

Primary tumors involving the Gasserian ganglion are rare and cannot be differentiated clinically from the metastatic tumor or the tumor involving the ganglion by contiguous growth. Davis and Martin[4] have reported 7 cases of meningiomas of the dural envelope of the Gasserian ganglion which produced the *paratrigeminal syndrome*. Cooper[2] has described 3 cases of primary tumor and Russell[12] reported 2 instances of endothelioma of the ganglion. Sachs,[13] Rand,[11] Krayenbuhl,[7] Dew,[5] Cohen[1] and Learmonth and Kernohan[8] all have reported primary tumors variously listed as endothelioma, sheath neuroma, neurinoma, neurofibroma and meningioblastoma. Case 1 in our series was thought to be a primary endothelioma of the ganglion and represented the only primary tumor in the group.

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Numerous reports in the literature concerning metastatic involvement of the Gasserian ganglion have appeared in the past 25 years. Occasionally encountered as a distant metastasis from adenocarcinoma of the breast, as reported by Fitzwilliams and Fell,[6] (case 2, our series) or other carcinomatous foci, the so-called *metastatic* tumor is, in most instances, an invasion of the ganglion by growth of the neoplastic cells via the perineural lymphatics or by contiguous growth from the paranasal sinuses, maxillas, oropharynx, or nasopharynx. The primary sites most frequently contributing to such invasion or extension are the maxillary region and the nasopharynx. In the former, the tumor of the maxillary area may come to involve the maxillary branch of the fifth nerve and by contiguous growth and extension along the perineural lymphatics ultimately invade the ganglion. Peet[10] records 2 cases in which this situation was reproduced, in 1 instance by carcinoma of the lateral ethmoid cell and in the other by tumor arising in the antrum. In our series, cases 7 and 10 represent examples of this type of ganglion involvement and cases 6 and 9 illustrate that similar situations may occur in tumors involving the mandible and the mandibular division of the fifth nerve.

When one considers malignancies of the Gasserian ganglion secondary to tumors of the nasopharynx it becomes obvious that too little attention has been paid to this frequent clinical complex, as point out by Woltman.[14] Adequate examination of the nasopharynx should be undertaken in all instances of unexplained facial pain of atypical type and in all cases of unexplained cranial nerve palsy. This has been re-emphasized by New,[9] who pointed out the striking lack of nasal and nasopharyngeal symptoms in most cases. As Dew[5] has stated, these tumors may be symptomless until they have extended beyond their original site in the pharyngeal wall, Rosenmüller's fossa, or Eustachian orifice. From this point erosion of the basiphenoid and extension into the foramina or orbital wall may occur. The following case summaries well illustrate the cardinal features previously emphasized.

CASE REPORTS

Case 1. M. H., a 62 year old woman gave a history of increasing left-sided facial pain, numbness and diplopia for five months. Examination revealed paresis of the left oculomotor nerve with diminished sensation over the entire left side of the face. The Gasserian ganglion was explored and an infiltrating tumor mass was removed from the ganglion and posterior root. All investigations for a possible primary site were negative. For the relief of pain the posterior root was sectioned by a posterior approach at a second operation.

Diagnosis: Endothelioma of Gasserian ganglion (fig. 1, case 1).

Case 2. M. W., a 40 year old woman, was admitted to the hospital with a history of having had a simple mastectomy for carcinoma of the breast one month previously. There had been severe pain in the right side of the face and right orbit for two weeks with progressive ophthalmoplegia. A subtemporal exploration revealed infiltration of the Gasserian ganglion and posterior root with neoplasm. The posterior root was divided for relief of facial pain.

Diagnosis: Adenocarcinoma of breast, metastatic to Gasserian ganglion (fig. 1, case 2).

Case 3. W. J. B., male, aged 52, was admitted to the hospital because of left-sided facial pain, tinnitus and diplopia of two months' duration. Examination revealed impaired sensation in the left side of the face in the area of the second and third divisions and a left abducens palsy. Exploration of the Gasserian ganglion revealed infiltration of the ganglion and posterior root with neoplasm. Examination of the nasopharynx postoperatively showed an invasive tumor in the left nasopharynx.

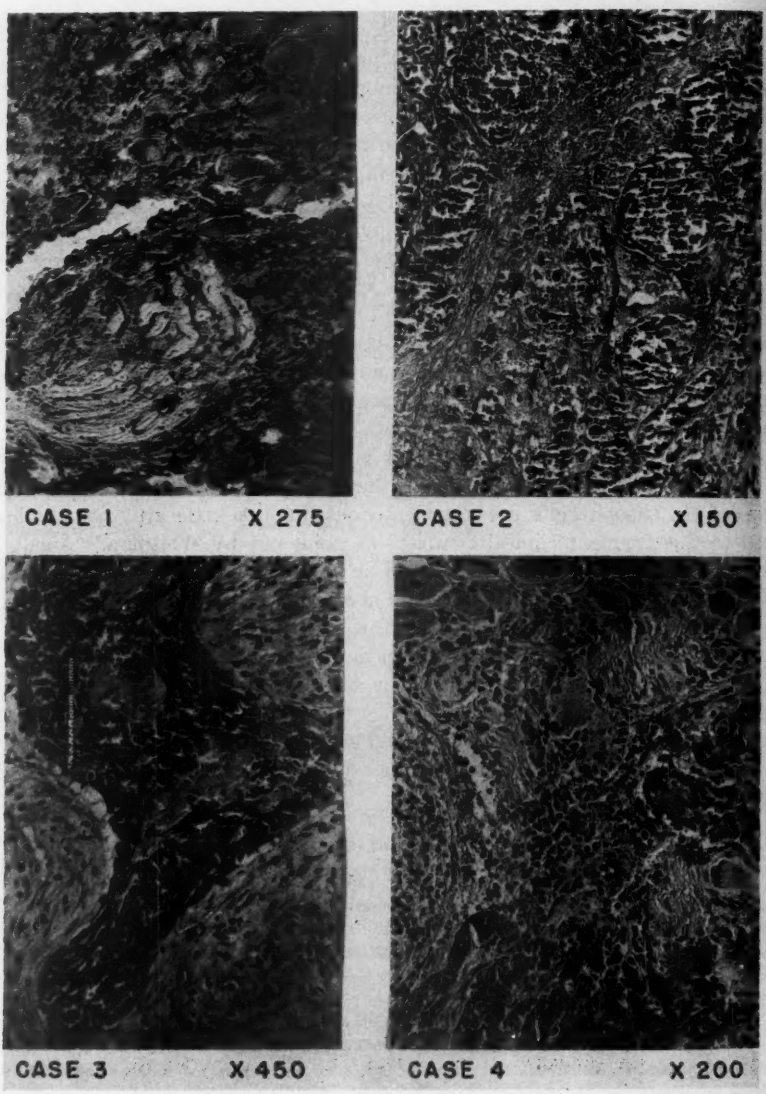

FIG. 1. Case 1. Endothelioma of Gasserian ganglion. Case 2. Adenocarcinoma of breast, metastatic to Gasserian ganglion. Case 3. Adenocarcinoma of nasopharynx, metastatic to Gasserian ganglion. Case 4. Squamous cell carcinoma of nasopharynx, metastatic to Gasserian ganglion.

Diagnosis: Adenocarcinoma of nasopharynx, metastatic to Gasserian ganglion (fig. 1, case 3).

Case 4. W. J. N., man, aged 54, was admitted to the hospital because of increasing right-sided facial pain for 12 months. For one month pain had been continuous with the development of numbness over the upper part of the face. The right ear felt *stuffy* and *popping*

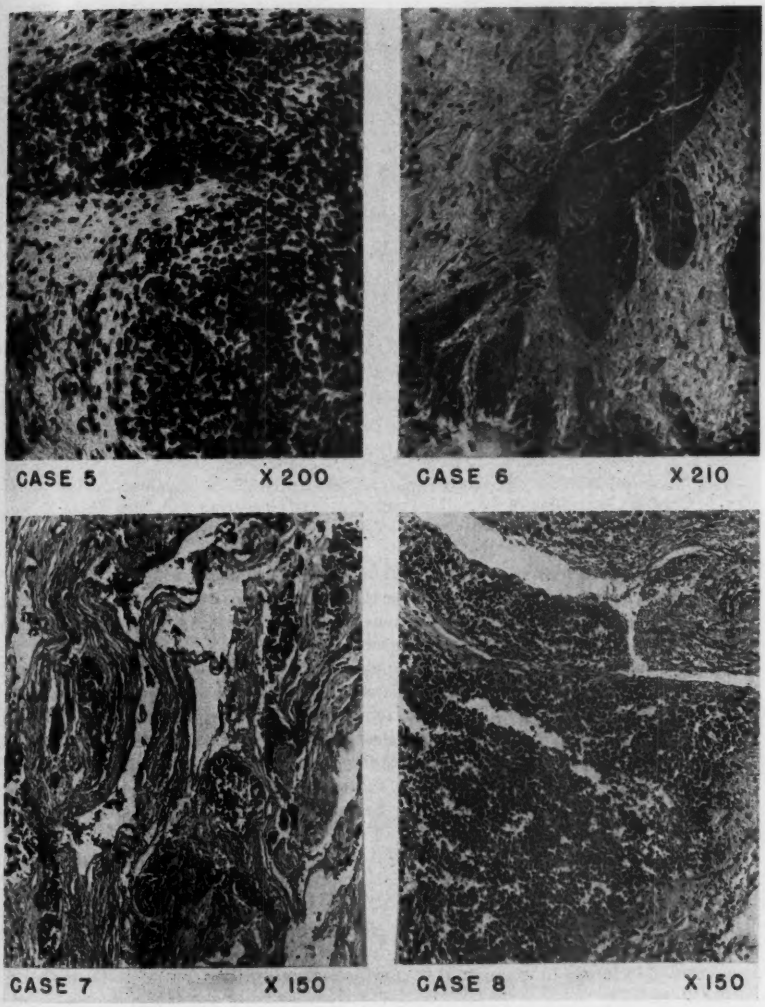

FIG. 2. Case 5. Carcinoma of sphenoid sinus, metastatic to Gasserian ganglion. Case 6. Squamous cell carcinoma of buccal mucosa, metastatic to Gasserian ganglion. Case 7. Carcinoma (oncocytoma) of maxilla and palate, metastatic to Gasserian ganglion. Case 8. Melanosarcoma of face, metastatic to Gasserian ganglion.

sounds were noted for about three weeks. There was motor and sensory fifth nerve impairment on the right. When the nasopharynx was examined, a tumor was found near the Eustachian orifice which proved to be a poorly differentiated squamous cell carcinoma. Deep roentgen ray therapy failed to relieve pain. Exploration of the middle fossa revealed a massive invasion of the Gasserian ganglion with tumor.

Diagnosis: Squamous cell carcinoma of nasopharynx, metastatic to Gasserian ganglion (fig. 1, case 4).

Case 5. E. L. B., man, aged 56, was admitted with a history of *sinus trouble* for six months. He experienced increasing pain in the left lower part of the face for six weeks, which was

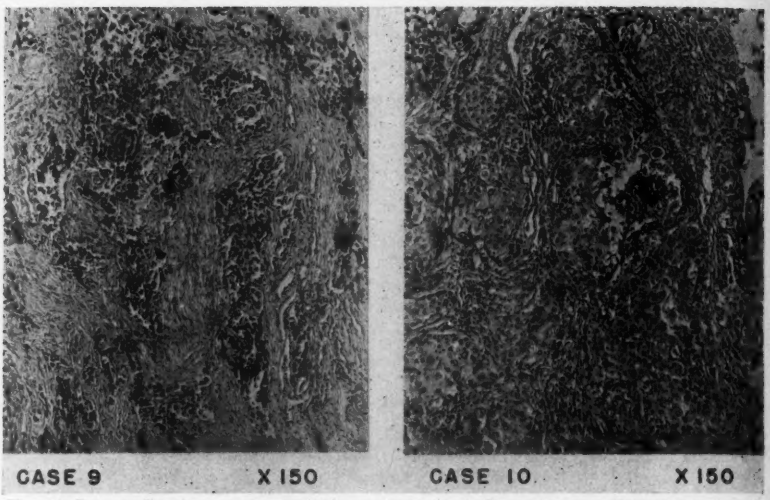

FIG. 3. Case 9. Carcinoma of mandible, metastatic to Gasserian ganglion. Case 10. Squamous cell carcinoma of buccal mucosa, metastatic to Gasserian ganglion.

followed by diplopia. There was partial oculomotor and abducens palsy on the left. Fifth nerve function was unimpaired. By posterior rhinoscopy a polypoid mass was found in the left sphenoid sinus. Biopsy revealed squamous cell carcinoma. Exposure of the Gasserian ganglion showed tumor invasion of third division and ganglion.

Diagnosis: Carcinoma of sphenoid sinus, metastatic to Gasserian ganglion (fig. 2, case 5).

Case 6. P. M. J., man, aged 52, was admitted to the hospital with a two year history of malignancy of lip and cheek with local excision followed by a radical neck dissection. Constantly increasing left-sided facial pain had been present for three months. There was sensory impairment in the distribution of the left fifth nerve. The posterior root of the left fifth nerve was divided with removal of a hard, infiltrating tumor within the ganglion.

Diagnosis: Squamous cell carcinoma of buccal mucosa, metastatic to Gasserian ganglion (fig. 2, case 6).

Case 7. J. G., woman, aged 42, was admitted to the hospital because of persistent pain in her entire face of eight months duration with numbness in the lower part of the face for eight weeks. Resection of superior maxilla was done two and one-half years previously for malignancy of maxilla and palate. Exposure of Gasserian ganglion revealed dense infiltration and replacement with tumor. The posterior root was sectioned for relief of pain.

Diagnosis: Carcinoma (oncocytoma) of maxilla and palate, metastatic to Gasserian ganglion (fig. 2, case 7).

Case 8. J. E. L., man, aged 56, was admitted to hospital with the history of having had a *cancer* of the right side of the face removed two years previously followed by increasing right-sided facial pain and burning paresthesias. The neurologic examination was negative. The posterior root of fifth nerve was sectioned and a large metastatic tumor mass was found lying in the dural envelope invading the ganglion.

Diagnosis: Melanosarcoma of face, metastatic to Gasserian ganglion (fig. 2, case 8).

Case 9. M. S., man, aged 74, was admitted to the hospital because of severe right-sided facial pain for 12 months. There was partial right fifth and seventh nerve palsy, and hard, fixed, right submaxillary lymph nodes. The roentgenogram showed erosion of the right mandible. Exploration of the middle fossa revealed extradural and intradural tumor about the ganglion with obvious enlargement of the third division due to tumor infiltration. The posterior root was sectioned.

Diagnosis: Carcinoma of mandible with metastasis to Gasserian ganglion (fig. 3, case 9).

[*Case 10.* I. M., woman, aged 74, was admitted to the hospital 13 months after resection of neoplasm of the left upper alveolus. For 10 months she suffered from increasingly severe pain in the left side of the face and left cheek which continued unabated. There was impaired sensory function of left fifth nerve. A roentgenogram showed enlargement of the left foramen ovale. Exploration of the Gasserian ganglion revealed infiltration of third division, ganglion, and posterior root with tumor. The posterior root was sectioned.

Diagnosis: Squamous cell carcinoma of buccal mucosa, metastatic to Gasserian ganglion (fig. 3, case 10).

DISCUSSION

It is obvious that the management of such cases of malignancy of the ganglion involves only an attempt to afford palliation. Roentgen ray therapy has given little significant relief of pain or prolongation of survival. Surgical exploration of the ganglion gives the opportunity to confirm the diagnosis, to remove tumor for microscopic confirmation, and at the same time to section the posterior root for more prolonged relief of pain. In only 1 instance was it impossible to completely section the sensory root due to distortion of the fibers by the tumor. In such a situation the root easily can be divided by approaching it through the cerebellopontine angle at a second operation (case 1). However, the relief obtained by any method necessarily is short lived and the problem remains therapeutically insoluble.

The rarer primary benign tumor of the Gasserian ganglion may, on the other hand, be removed completely and a permanent cure effected.

CONCLUSION

It is hoped that the presentation of this series of cases will again emphasize the importance of constant clinical alertness regarding the significance of chronic atypical facial pain, particularly when associated with impairment of cranial nerve function.

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INTRANASAL ENCEPHALOCELE: A CASE REPORT

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Imperfect closure of the neural tube, resulting in spina bifida or cranium bifidum is probably the most common of all congenital anomalies. Up to one-fourth of all infants may have some such defects, usually in the lumbosacral spine.[6] In about 1 of each 1000 infants there is a lesion of clinical significance, a meningocele, myelomeningocele, or encephalocele.[1] About 10 per cent of these affect the meninges only and present no serious problem of treatment. In the large proportion of patients where the spinal cord is involved, treatment is difficult and the salvage rate is low.[5] The defect is cranial in some 10 to 16 per cent.[3] The occipital region is the most common site, but the lesion may be in the vertex, forehead or cribriform plate. The nasal encephalocele which accompanies this defect of the floor of the anterior fossa is of special interest because of the unique problem of differential diagnosis and also because of the prospect of an excellent outcome of treatment.

An intranasal encephalocele was first reported by Richter[7] in 1813. Gisselsson[2] in 1947 was able to find 34 reported cases and 13 more were added by Moore[4] in 1952. Most of the cases were discovered when cerebrospinal fluid rhinorrhea followed removal of a nasal mass erroneously diagnosed as a polyp. Before antibiotic or sulfonamide therapy was available, death from meningitis nearly always followed. In recent years, however, surgical repair of the dural defect has been done in several patients and recurrent meningitis following nasal excision has been combated successfully.[4] In the case to be reported focal irritation of the brain developed at the site of infection.

CASE REPORT

J. R. W., a 21 months old boy entered the hospital on the service of Dr. Cobb Pilcher Feb. 21, 1949 because of focal convulsive seizures and weakness of the right arm and leg. He was born at full term, the first child of a 39 year old mother and a 65 year old father. At birth, a cyst was noted in the left nostril. This became larger, actually protruding from the nose after two weeks and at this time was removed surgically. The mass recurred after several weeks and again was removed at the age of 6 weeks and at 2 months. At the age of 4 months an extensive removal was done with coagulation of the base. Microscopic examination showed "chronic inflammation with cystic membrane." After this operation almost constant watery rhinorrhea was noted by the parents. Three more nasal operations were done up to the time of admission. There were frequent upper respiratory infections, which were treated with sulfonamides and penicillin. At the age of 12 months, during an acute, febrile illness, right sided focal convulsions occurred. Each attack began with twitching of the eyes and the right side of the face, spreading to the right arm and leg. Over a period of six weeks, during which time he received intermittent chemotherapy, there were exacerbations of fever

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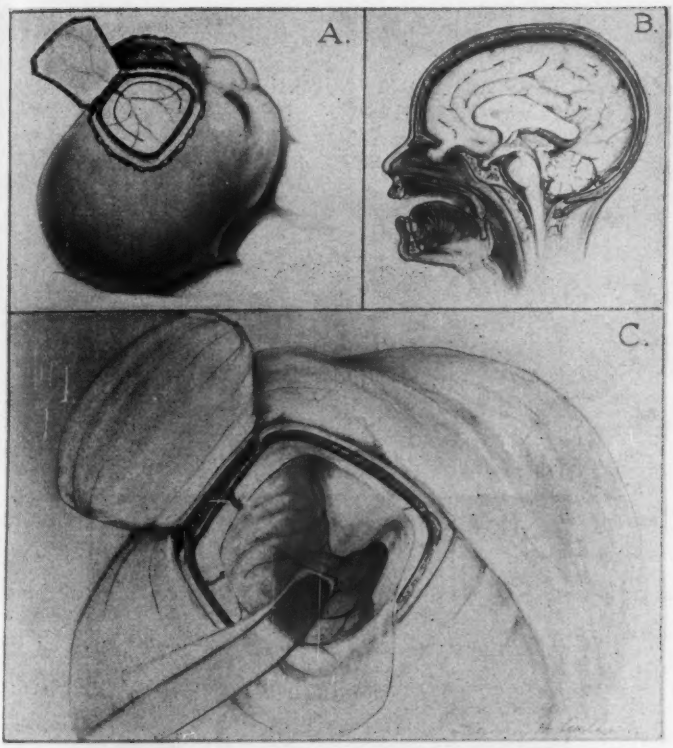

FIG. 1. A. Left frontal craniotomy. B. Schematic section to show position of encephalocele and the nasal cavity. C. Stalk of frontal lobe entering defect at the cribriform plate.

with extreme restlessness and frequent severe right sided convulsions, at times lasting as long as four hours and requiring heavy sedation. During the next eight months, up to the time of admission, he continued to have intermittent fever and occasional convulsions. Unsteadiness in walking and weakness of the right leg developed gradually during this period.

Examination revealed a well developed slightly retarded child with a broad nose and constant watery discharge from the left nostril. A small boggy mass could be seen in the left ethmoid area. There was partial fusion of the third and fourth toes bilaterally. Neurologic examination was negative except for unsteadiness in walking with a slight tendency to drag the right foot. Roentgenographic examination of the skull and sinuses was negative. The spinal fluid pressure, cell count and protein were normal. Fluid from the left nostril contained 94 mg. per cent sugar. Electroencephalogram showed 5 per second sinusodal waves occurring in bursts in uniploar leads, and some slow spike variants. There was no definite asymmetry.

Operation.—Feb. 28, 1949. A left frontal craniotomy was made (fig. 1-A), and as the frontal lobe was elevated a neck of brain tissue was seen entering the nose. This was coagulated and cut across exposing an opening in the position of the cribriform plate (fig. 1-B). Several layers of gelfoam were placed over the opening and a small flap of dura was sutured across it. Needle exploration of the left frontal lobe failed to disclose an abscess. Histologic

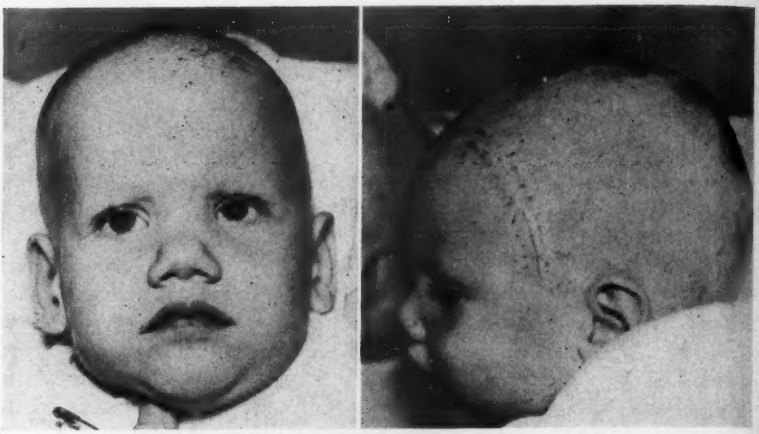

FIG. 2. One week after operation

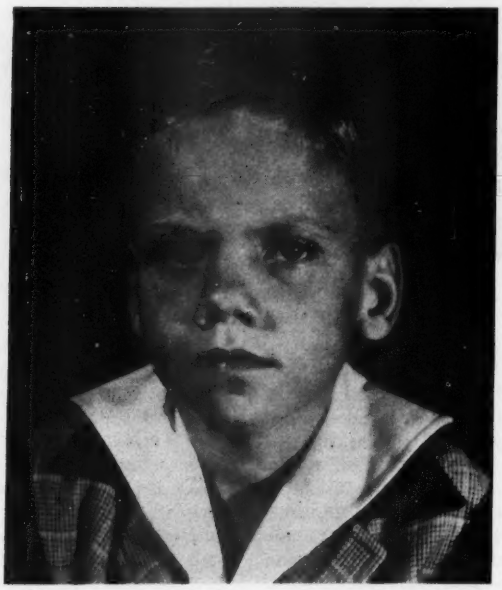

FIG. 3. Sept. 13, 1952, age 5 years

examination of a fragment of the stalk of brain tissue showed moderate gliosis. A few ganglion cells were present.

Course.—He recovered satisfactorily and has been followed closely up to the present time, April 1, 1954 (figs. 2 and 3). There have been no seizures, mental development is normal and his gait is steady. An electroencephalogram made on Jan. 19, 1950 was normal. A small boggy mass could still be seen high in the nose but there was no rhinorrhea.

DISCUSSION

The danger of meningitis long has been realized in cerebrospinal fluid rhinorrhea. Small nasal encephaloceles, if amputated, may lead to this complication. In the present case focal epilepsy followed a series of attacks of meningitis, each arrested by antibiotic therapy. After intracranial repair of the dural defect and amputation of the cerebral stalk, the patient recovered fully. To our knowledge this is the first patient in whom this complication has been arrested.

SUMMARY

A case of nasal encephalocele is reported in which focal epilepsy followed a series of episodes of meningitis.

Encephalocele should be considered when a cystic lesion of the nose is seen in early childhood. Abnormal width of the nose or forehead and the finding of a sugar content of the fluid similar to that of spinal fluid support the diagnosis.

The occurrence of meningitis after rupture of a nasal encephalocele does not preclude successful treatment.

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MIXED TUMORS OF THE SALIVARY GLANDS

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The principal purpose of this article is to present the follow-up data on 64 patients with mixed tumors of the salivary glands treated in the Vanderbilt University Hospital from 1925 through 1949.

INCIDENCE

Sixty-nine mixed tumors of salivary glands have been removed in this institution, but since our efforts to follow 5 of them were unsuccessful, the discussion will be limited to the remaining 64 patients.

There were 42 females and 22 males. The average age of the patients at the time of admission was 41.5 years with a range of 20 months to 79 years. The average duration of the presence of the mass was 9.5 years. Although the majority of the tumors were found in the parotid region, they were also seen in the region of the submaxillary gland, the hard and soft palate, the antrum and the alveolus (table I).

TREATMENT

Because of the facts that mixed tumors continue to increase in size, although usually slowly; that possibly carcinoma can arise in a mixed tumor, and that one cannot be certain of the benignancy of such a tumor until it is seen under the microscope, we believe that all of them should be excised. We now believe that mixed tumors are radio-resistant and agree with Janes[3] that cures by radiation therapy are rare or nonexistent. Furthermore, following roentgen ray therapy, 1 of our patients developed radiation necrosis of the maxilla; another had osteomyelitis of the mandible and both had intractable pain.

Although simple excision may seem adequate in small tumors, it is possible that small tentacle-like extensions—invisible grossly—may be left behind, and our high recurrence rate leads us to believe that superficial lobectomy may be the minimal justifiable procedure in all mixed tumors of the parotid. Other factors which support this belief are that such tumors may be of multicentric origin; that recurrences are usually near the site of the original lesion, and that some observers have found carcinoma in 20 per cent of such tumors. The details of the operation of superficial lobectomy of the parotid have been described by Bailey,[1] Byars,[2] Janes[3] and State.[9] When this procedure is done the entire side of the face must be left uncovered by drapes in order to observe any twitching which may occur when a nerve filament is disturbed. Before the excision is done the facial nerve must be identified. It may be exposed at the stylomastoid foramen

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TABLE I

Distribution of tumors

Location	Number
Parotid	47
Submaxillary	4
Hard and soft palate	9
Antrum	2
Alveolus	2

or at the interval between the anterior border of the superficial lobe and facial nerve branches at the point where the parotido-masseteric fascia becomes thin. Knowledge of the relationship of the posterior facial vein to the lower division of the facial nerve aids in the dissection of the isthmus from either the anterior or posterior approach. Our high recurrence rate in recurrent tumors—several patients having from three to five recurrences in the superficial lobe—indicates to us that superficial lobectomy should be done for recurrent tumors. In some instances perhaps total parotidectomy may be indicated.

COMPLICATIONS

In 14 patients some degree of facial nerve injury occurred. However, all of these were in the less cosmetically important cervicofacial division and only three were permanent mandibular branch injuries. Two of the three permanent injuries occurred in operations for recurrent tumors. The other 11 injuries ranged from the effects of trauma, which disappeared shortly, to complete paralysis, the latter probably being relieved because of the existence of the frequent cross anastomoses in the distal filaments of the facial nerve. The anatomic studies of McCormack and his associates[4] indicate that, in injury to minor facial nerve elements, the fairly common return of function occurs because of these anastomoses.

Although Slaughter[8] stated that of 55 patients with carcinoma of the parotid 12 arose in previously benign tumors, we found only 1 such instance. The Fry syndrome of gustatory sweating did not occur in any of our patients nor did any of them develop a salivary fistula.

FOLLOW-UP DATA

McFarland[6] demonstrated the fact that, by studying the microscopic sections of mixed tumors, pathologists were only 50 per cent correct in their predictions of the possibility of recurrence. We attempted such predictions and found ourselves unable to do it with any degree of accuracy. The possibility of multicentric origin of mixed tumors is suggested by the presence of pea-sized nodules occasionally seen near the larger tumor (McFarland[5, 6] and McNealy and McCallister[7]) and by recurrences which do not appear until many years after the primary excision.

Sixty-four patients were followed for an average length of time of 11.3 years, 31 of them being followed for more than 11 years and 17 being followed for more

TABLE II

Recurrences of mixed tumors

Type Tumor	No. Cases	No. Recurrences	Per Cent Recurrences	Average Follow-Up
All patients	64	19	30.6	11.3 years
All primary	52	11	21.1	
All recurrent	12	8	66.6	
All parotid	47	12	25.5	
Capsule ruptured	25	5	20.0	10.3 years

than 15 years. There were 19 recurrences or 30.6 per cent in the 64 patients (table II). In the 52 patients who had operations for primary tumors there were 11 (21.1 per cent) who had recurrences. The average time between operation and recurrence in primary tumors was 9.0 years and the interval was 20 years in 1 patient (table III). The recurrence rate in mixed tumors of the parotid only was 25.5 per cent and in the 12 patients who had operations for recurrent tumors (table IV) there were eight recurrences (66.6 per cent). Most of the latter group were not subjected to superficial lobectomy or total parotidectomy. The average time from the second operation to the second recurrence was 5.2 years.

The longer the follow-up period, the higher we found the recurrence rate. In the entire group the recurrence rate probably would have been even higher than the 30.6 per cent recorded except for the fact that 10 of them were followed less than the average length of time at which recurrence was noted, that is, 7.5 years. Six of the 10 were operated upon from four to seven years before the follow-up study was closed and 4 died of other causes less than seven years after operation. In the patients who were followed eight years the percentage of recurrences was 44 and in those followed 11 or more years it was 48.6.

TABLE III

Recurrences of primary tumors

Patient	Location of tumor	Time of recurrence
S P - 248	Parotid	11 years
S P - 4902	Parotid	15 years
S P - 5663	Parotid	11 years
S P - 6449	Parotid	7 years
S P - 7948	Alveolus	7 years
S P - 8490	Parotid	20 years
S P - 15985	Parotid	8 years
S P - 17845	Parotid	8 years
S P - 19548	Parotid	4 years
S P - 23170	Palate	4 years
S P - 25731	Parotid	3 years
Average time of recurrence		9.0 years

TABLE IV

Recurrences in recurrent tumors

Patient	Location of tumor	Time of recurrence
S P - 889	Parotid	1 year
S P - 2231	Antrum	13 years
S P - 9792	Submaxillary	4 years
S P - 12824	Parotid	13 years
S P - 15527	Submaxillary	0.5 year
S P - 23331	Palate	1 year
S P - 25525	Parotid	1 year
S P - 20516	Palate	8 years

Rupture of the capsule failed to increase the recurrence rate (table II). In 25 instances this occurred, varying from a slight tear during traction to piecemeal removal, but in all instances the surgeon thought that all of the tumor was removed. In these 25 patients there were five recurrences or 20 per cent, actually less than in the entire group. The average length of follow-up of these patients was 10.3 years.

If there are included the operations done elsewhere, the recurrence rate rises from 30.6 per cent to 34.5 per cent. If one included the multiple recurrences found in several patients, there were 39 recurrences in 64 patients.

The fact that five years without recurrence is too short a time to denote *cure* of mixed tumors is shown by the facts that the average length of time between operation and recurrence was 7.5 years; that nine of the 19 recurrences were noted after eight years and that one was found after 20 years. To us this indicates that these tumors are sometimes of multicentric origin and that the recurrence is not always a persistence of the original tumor but actually a new one.

SUMMARY

Sixty-four patients with mixed tumors of the salivary glands have been followed for an average length of time of 11.3 years with a recurrence rate of 30.6 per cent.

CONCLUSIONS

A five year follow-up will fail to give the true recurrence rate of mixed tumors.

Because of the high recurrence rate in primary mixed tumors and the higher recurrence rate in recurrent mixed tumors, we think that superficial lobectomy may be indicated in the former and almost certainly is indicated in the latter group.

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LIPOID GRANULOMA OF THE LUNG

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The high incidence of carcinoma of the lung has encouraged surgeons during recent years to advise exploratory thoracotomy for pulmonary lesions when the diagnosis cannot be established within short periods of time following their discovery. The failure clearly to demonstrate the nature of pulmonary tumors by examinations of the sputum, bronchoscopic examination and careful roentgenographic study often leads to the belief that the lesion is malignant in nature and more often than not such an assumption will prove to be correct. Certain chronic inflammatory lesions so closely may simulate carcinoma of the lung, however, that the distinction may be difficult or impossible even at the time of operation. Atypical forms of tuberculosis and chronic suppurative pulmonary infections very occasionally may be mistaken for carcinoma. During the last seven years we have encountered pulmonary lipoid granuloma with increasing frequency and in 5 patients pneumonectomy has been peformed by us because of the belief that the lesion might be neoplastic. It is the purpose here to discuss some of the aspects of chronic lipoid pneumonitis, especially as it is related to the differential diagnosis of carcinoma and to report 7 cases of the disease.

PATHOGENESIS

All oils which are introduced into the lungs are irritating to some degree. Various oils of animal and vegetable origin especially are deleterious. Mineral oil is a light, bland oil which usually will not excite the cough reflex and is neither absorbable nor assimilable. Laughlen[5] was the first to show that mineral oil, when administered through the nose or mouth, will find its way to the alveoli without effort to make it do so. Predisposing factors which lead to the aspiration of oil include anatomic defects in the mouth, palate, tongue, larynx or esophagus; neurologic disturbances which interfere with swallowing; senility and generalized debility and the forced feeding of fats in infants and psychotics. The use of oily nose drops and throat lubricants by healthy persons can cause lipoid pneumonia. As a result of the work of Cannon and Walsh,[2] the American Medical Association's Council on Pharmacy and Chemistry in 1942 omitted from New and Nonofficial Remedies all types of nasal inhalants containing liquid petrolatum because of the danger of lipoid pneumonia and because isotonic aqueous solution could do equally well.

Chronic lipoid pneumonia in adults caused by oils taken orally usually results from the repeated ingestion of mineral oil or other petrolatum products. Laxa-

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tives usually are administered at night and a few drops of bland oil easily may find their way from the pharynx, the stomach, or the lower esophagus into the trachea of a normal person during sleep, and reach the alveoli. Over a period of time considerable mineral oil may reach the alveoli, the patient being unaware that oil has been repeatedly aspirated.

Mulvaney[8] first described the use of mineral oil for medicinal purposes in 1869. In a patient with obstructing *erysipelatous laryngitis* he "by means of an atomizer, threw about a drachm of coal oil, in the form of a spray into the larynx and trachea every two hours." Rosenberg,[11] in 1885 and 1887, advocated the intranasal use of olive oil and menthol in the treatment of tuberculous laryngitis. Waters, Bayne-Jones, and Roundtree[13] pointed out, in 1917, the possibility that oils, which then were occasionally administered intratracheally in the treatment of tuberculosis, bronchiectasis and other chronic pulmonary infections, might be detrimental.

Laughlen,[5] in 1925, reported the first cases of lipoid pneumonia in human beings. Three of his 4 cases were in children and in all of the cases menthol and mineral oil had been used. Pinkerton,[9] in 1927, reported the first classic studies of the reactions of oils and fats on pulmonary tissues. Ikeda[3] first described lipoid pneumonia of the adult type, or paraffinoma of the lung, in 1937, and distinguished this from an earlier type of oil pneumonitis, called the infantile type of lipoid pneumonia. Now there are in excess of 400 cases in the literature reported by many workers. Janes,[4] in 1947, reported 2 cases of lipoid pneumonia simulating bronchogenic carcinoma. This was the first report of the difficulty in differential diagnosis and stimulated the interest of thoracic surgeons in this disease. Berg and Burford[1] in 1950 reported 6 cases of lipoid pneumonia requiring surgery for a differential diagnosis.

Robbins and Sniffen[10] and Waddell, Sniffen and Sweet[12] have called attention to the fact that cholesterol and cholesterol esters may be found in abundance in certain chronic inflammatory lesions of the lung which closely may simulate carcinoma. They question the idea that this type of chronic pneumonitis is a primary entity and suggest that bronchiolar obstruction, found in some of their cases, may be the determining factor in leading to the deposition of these sterols in the tissues. Morgan[6] states that the source of these lipids (sterols) probably is inflammatory exudate and he believes that lipoid pulmonary disease may not be exogenous as often as has been previously thought. We recognize the existence of the pathologic entity described by these authors but this report is concerned only with exogenous lipoid pneumonia. Cases in which the endogenous type of lesion has been found following lobectomy or pneumonectomy have been discarded from this study.

PATHOLOGY

Exogenous lipoid granuloma is thought to be most commonly located in the more dependent portions of the lungs and often has been reported to be bilateral. However, Muether,[7] Janes and others have reported cases where the lesions were localized exclusively in the upper lobes of the lungs. In the 7 cases

reported below, the upper lobe was involved in 4 and in 2 others both the upper and lower lobes were diseased. All were unilateral.

The lesions are firm, diffuse or nodular and can vary in size from a few millimeters to the diffuse involvement of an entire lung. On cut surface oil may extrude and be present on the knife. The color is either white, grey or yellow depending on the age of the lesion. Where the oil is entrapped in hyaline fibrous tissue containing little or no air the lesion has been called a *paraffinoma*.

On reaching the alveoli the oil first becomes emulsified and most of it is phagocytized by large macrophages called *foam cells* or *lipophages*. The alveolar epithelium becomes cuboidal and several layers thick. Inflammatory exudate then enters the alveoli, and occasionally some inflammation of the bronchial mucosa and peribronchial tissues also develops. Later a reticulum of collagenous fibers develops between the macrophages within and about the alveoli, and the oil gradually becomes fixed in fibrous tissue, thus obliterating many air spaces. During this phase of progressive fibrosis small droplets of oil may coalesce to form rather large oil filled spaces within the scar tissue. Within the fibrous tissue and surrounding groups of lipophages may be found areas of necrosis encircled by giant cells and epitheloid cells resembling tubercules, which give the microscopic picture of a granuloma.

Oil reaches the lymph nodes in the region of the hilum of the lobe and occasionally within the mediastinum and considerable enlargement of these nodes has been noted by us. In time, these lymph nodes become partially replaced by dense fibrous tissue and this change is accompanied by adjacent progressive scarring which fixes the hilar nodes about the bronchus and vessels into a hard mass which may be difficult or impossible to distinguish from carcinoma. It must be borne in mind that the growth of cancer—when it is slow—may excite fibroblastic proliferation to such a degree that it cannot be distinguished grossly from chronic inflammatory lesions unless the tumor is sectioned and examined microscopically. Such a procedure is, in our opinion, unwise at the time of exploratory operation because cure of visceral carcinoma by surgical excision is dependent upon the employment of the principle of complete extirpation of the lesion without the exposure of tumor tissue.

The classification of this disease into *infantile* and *adult* types, first clearly defined by Ikeda, clinically may be useful in distinguishing the acute— and sometimes fatal—type of pneumonia seen in infants and children, from the so-called *adult* type of paraffinoma with which this paper is concerned. The differences in the pathologic pictures observed may be due in part to the type of exogenous oil or fat which causes the inflammation, that is, whether of animal, vegetable or mineral origin. The infantile type of lesion differs from the adult type because the former is violent, widespread and of relatively short duration. The infantile type is observed, at times, when true hepatization is present. The pathologic picture observed in the *adult* lipoid pneumonia or paraffinoma, on the other hand, represents the inflammatory changes which inevitably accompany the prolonged reaction to the presence of foreign material. The adult type is a granulomatous lesion in which the damage to the lung is permanent and which represents the

natural end result of the presence of a bland oil which has become fixed in the tissues.

The clinical and pathologic pictures produced by mineral oil differ markedly, then, from those produced by other fats or oils, such as cod liver oil, in that the mineral oil granuloma is essentially a slowly but persistently progressive foreign body reaction whereas the *infantile* lipoid pneumonia is a more violent inflammatory reaction accompanied by exudation, necrosis of tissues, widespread hepatization and finally resolution of much of the process in the event the patient survives.

CASE REPORTS

Case 1. M. B. S., a 54 year old white man, entered Vanderbilt University Hospital Aug. 21, 1947 complaining of weakness and weight loss. He had been in good health until one year prior to admission when he began to loose weight and have chronic fatigue. He had some shortness of breath which was relieved by change in position. There had been no hemoptysis, chills or fever. He was found to be anemic by his local physician and was given two blood transfusions prior to admission to the hospital. He had taken mineral oil regularly for many years for chronic constipation.

Physical examination showed a well developed, thin, white man whose chest was clear to percussion and auscultation on the left. On the right there were decreased breath sounds in the base and axilla extending up to the fifth rib posteriorly.

Roentgenologic findings consisted of an area of increased density in the right base adjacent to the heart border which presented a convex border laterally and which on lateral film was seen to lie in the region of the right middle lobe ((fig. 1). The preoperative diagnosis was bronchogenic carcinoma.

Bronchoscopy and exfoliative cytology studies were negative.

At operation, the patient was found to have a hard, nodular tumor mass which involved the entire middle lobe and a large part of the lower lobe and also a portion of the upper lobe. The tumor extended into the hilar region of the lung and was densely adherent to the pericardium over a wide area. A right pneumonectomy was done.

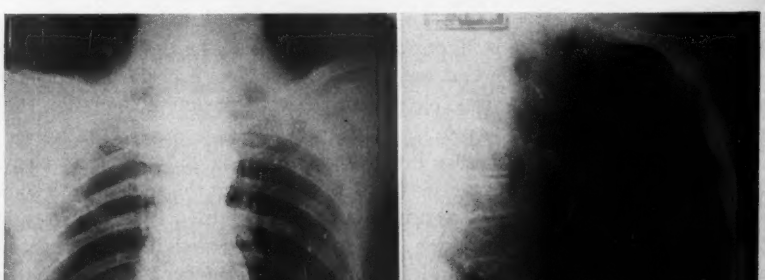

FIG. 1. Case 1. Roentgenograms which show changes suggestive of atelectasis of the right middle lobe.

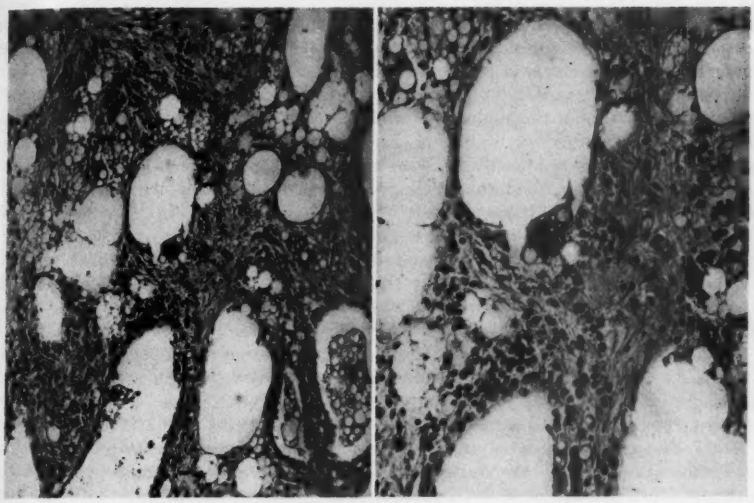

FIG. 2. Case 1. Low and high power photomicrographs which reveal the granulomatous process. Giant cells which contain oil droplets and large tissue spaces occupied by oil are shown.

The lung weighed 597 Gm. A portion of the pericardium 8 by 3 cm. in size was attached to the middle lobe. The middle lobe was completely consolidated and was densely adherent to a hard, irregular mass which occupied the anterior aspect of the lower lobe and which was approximately 6 cm. in diameter. Cut section revealed hard, greyish-white tissue which had replaced nearly all of the middle lobe and a portion of the lower.

Microscopic sections showed a remarkable variety of lesions, all thought to represent a reaction to aspirated lipid material (fig. 2). The changes were those of a granulomatous process varying in chronicity and degree from area to area, and being considerably more advanced in some zones than in others. The visceral pleura was thickened and there was a diffuse subpleural infiltrate of chronic inflammatory cells and some fresh blood. Adjacent to the visceral pleura in one section was seen a thick layer of collagenous tissue showing some hyalinization and hemorrhagic infiltration, fatty tissue, and a diffuse infiltration of round cells, occasionally clumped.

The changes throughout appeared to have originated within the air sacs and to have spread to involve the alveolar septa, so that the septa generally were much thickened. In the areas of more acute reaction, the alveolar spaces contained acute inflammatory cells, chronic inflammatory cells, lipoid-laden macrophages, and small vacuoles of free lipid material; occasional small foci of polymorphonuclear leukocytes and necrotic debris were also present. The septa themselves were infiltrated with acute and chronic inflammatory cells and many lipoid-laden macrophages. Often these macrophages were filled with a single fat globule. In addition, there was commonly noted a cuboidal, metaplastic alteration of the alveolar lining cells, and many of the alveoli were lined by large foreign-body type giant cells, often fused. Similar cells commonly were seen within the septa. In many areas, the inflammatory reaction was less severe surrounding the macrophages with engulfed fat. Numerous air sacs were filled with whorls of moderately dense scar tissue which obliterated various sized zones of pulmonary parenchyma by confluency. Within these areas of scarring were numerous vacuoles of varying size, surrounded by inflammatory cells and foreign body type giant cells. Diffuse infiltration of these areas with chronic inflammatory cells and often accumulations of round cells suggesting small lymphoid follicles were noted. Considerable fresh

hemorrhage was seen, especially within the alveolar spaces, as well as innumerable granulomata of varying size containing lipoid-laden macrophages. One section contained a rather large area of tissue necrosis surrounded by a zone of inflammation.

The arterial walls generally were moderately to markedly thickened, and there was some degree of vacuolation of the subintimal cells. Many of the smaller bronchi were irregular and surrounded by a conspicuous inflammatory infiltrate. Occasionally the bronchial lumens contained fat droplets and fat filled macrophages. One large bronchus was filled with amorphous debris, numerous polymorphonuclear leukocytes, and macrophages and the bronchial wall itself was irregularly destroyed.

Case 2. J. L., a 72 year old white man, entered Vanderbilt University Hospital July 19, 1950 complaining of cough and weight loss of six weeks duration. Cough was productive of yellow sputum. He had occasional wheezing. There was no hemoptysis. He had had slight anterior chest pains bilaterally and slight hoarseness. He had taken mineral oil regularly for many years.

Physical examination revealed an elderly, thin, white man whose chest showed dullness to percussion and diminished breath sounds in the right base. There was no clubbing of the fingers.

Roentgenograms showed a dense shadow in the region of the middle lobe.

Bronchoscopy was noncontributory. Bronchial washings for exfoliative cell study showed large macrophages which were vacuolated in such a manner as to suggest that they contained fat. There were no neoplastic cells seen. The preoperative diagnosis was bronchogenic carcinoma.

At operation there was found a large, nodular, hard mass in the region of the hilum of the right lung which involved the middle lobe to a greater extent than any other portion of the lung, but which also extended into the hilar structures of the upper and lower lobes. The lesion, being nodular and extremely hard, was thought to be neoplastic and it was thought that incision into the tumor should not be made for the purpose of microscopic diagnosis. A right pneumonectomy was done.

On pathologic examination, the right middle lobe showed almost complete replacement of the parenchyma by an indurated mass and the lobe appeared to be atelectatic. Yellow ap-

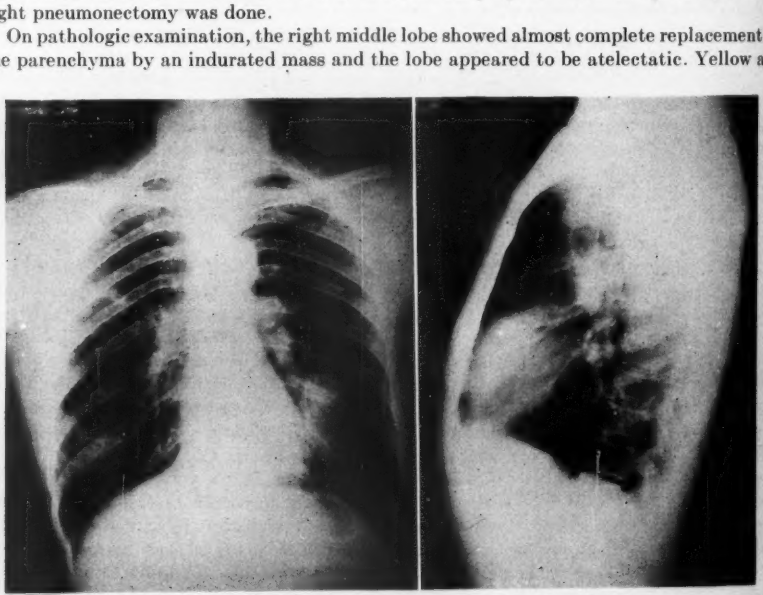

FIG. 3. Case 3. Roentgenograms which reveal an area of density in the region of the lingula segment of the left upper lobe.

pearing solid material could be expressed from the lower lobe bronchus. On cut section the mass was firm but not stony hard and was not encapsulated. It was grey in color and appeared to be homogenous throughout. No cystic areas were present. Microscopic examination revealed a typical paraffinoma which stained with Sudan III and not with osmic acid.

Case 3. L. F. A., a 57 year old white woman, entered Vanderbilt University Hospital Aug. 8, 1950 complaining of sharp pains in the left lower anterior chest of eight weeks duration and a cough productive of foul smelling sputum, which was worse in the mornings. She had occasionally noted small flecks of blood in the sputum. She had taken mineral oil and used oily nose drops intermittently over a period of many years. The mineral oil was always taken at bedtime.

Physical examination revealed a well developed, well nourished white woman whose chest was clear to percussion. Breath sounds were diminished at the left base. There were no rales, friction rubs, cyanosis or clubbing of the fingers.

Roentgenologic findings consisted of a homogeneous density in the region of the lungular segment of the left upper lobe (fig. 3).

Bronchoscopy was noncontributory.

At operation the lingular segment of the left upper lobe was found to be firm and rubbery in consistency. There was also a superficial area of scarring involving the pleura of the left upper lobe. The lingular segment of the upper lobe was excised.

Pathologic examination showed the pleural surface to be shiny and smooth. The entire segment was homogeneously firm. In the middle of the specimen there was an area of greyish brown discoloration which was not clearly demarcated from the remainder of the lung.

Microscopic examination revealed a typical lipoid granuloma (fig. 4). The oil stained with Sudan III. The moist weight of the fixed specimen was 255 Gm.; 15 Gm. of oil were extracted and identified as pure mineral oil.

Case 4. A. F. K., a 54 year old white man, entered Vanderbilt University Hospital July 13, 1953 complaining of chest pain, chills and fever of four weeks duration and of a nonproductive dry cough of two weeks duration. He had had frequent lower respiratory infections for many years and on five occasions was said to have had pneumonia. He had had no hemoptysis. He previously had been sent to a tuberculosis hospital but subsequently was dis-

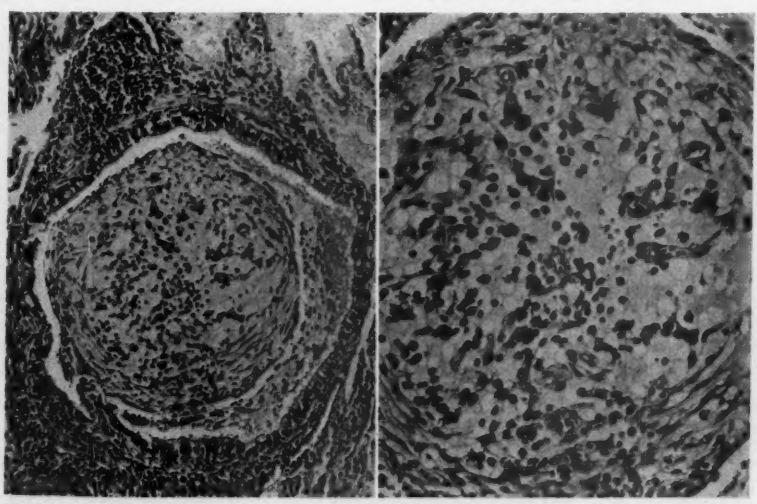

FIG. 4. Case 3. Low and high power photomicrographs which show a chronic inflammatory process. Macrophages which contain oil droplets are present.

charged as nontuberculous. He had taken mineral oil intermittently at bedtime for many years and used "Vicks Vapor-rub" nightly for 20 to 30 years for drying of his nostrils.

Physical examination showed a thin, white man whose chest was clear to palpation, percussion and auscultation. There was no clubbing of the fingers.

Roentgenologic findings consisted of bilateral emphysematous lungs and a confluent, homogenous density in the left apical region which had the appearance of atelectasis and which was thought to be due to bronchogenic carcinoma.

Bronchoscopy was noncontributory. Exfoliative cytology studies were negative. A differential diagnosis of lipoid pneumonia was made.

At operation, the lesion was found to involve the distal portion of the left pulmonary artery and its branches in such a way that the upper lobe artery could not be freed except by section of the tumor mass. In trying to free the upper lobe artery, a large tear was created in the left main olmonary artery and a pneumonectomy was done subsequently

Pathologic examination revealed a firm mass 5 by 4 by 5 cm. in the upper lobe, peribronchial in location. The lesion cut with firm resistance and had the gross appearance of carcinoma. Microscopic examination showed a typical paraffinoma which stained with Sudan III and not with osmic acid.

Case 5. R. G. L., a 65 year old white man, entered Vanderbilt Hospital Oct. 19, 1953 complaining of a chronic cough productive of a large quantity of yellow sputum and the loss of 30 pounds in weight. His illness began two years prior to admission. He had had afternoon rises in temperature. Eight weeks prior to admission he experienced the gradual onset of a constant, dull, aching, nonradiating pain in the anterior portion of his left chest. He noted a trace of blood present in his sputum about one month prior to admission. He had taken mineral oil as a laxative almost every night for five or six years. He had not used oily nose drops.

Physical examination revealed a thin, undernourished white man whose chest was clear to percussion. The breath sounds on the left were harsh but no rales were heard. Vocal and tactile fremitus were normal.

Roentgenologic findings consisted of a somewhat homogenous density extending lateral and slightly upward from the hilar region on the left. In the lateral view the area of infiltration occupied the region of the apico-posterior segment of the left upper lobe. An irregular area of radiolucency was present in the plane of the first anterior interspace with scattered

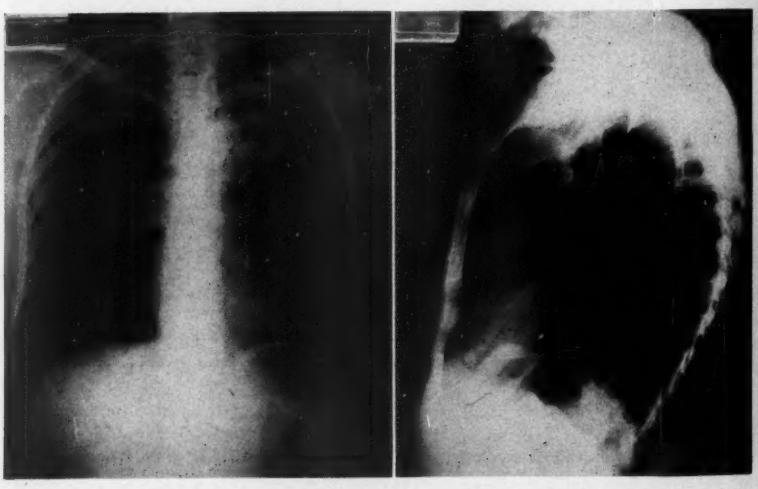

FIG. 5. Case 5. Roentgenograms of the chest. Extensive disease of the left upper lobe.

smaller areas of rarefaction scattered about it, suggesting the presence of multiple cavities. There was evidence of bilateral pulmonary emphysema.

Bronchoscopy was noncontributory.

The preoperative diagnosis was bronchogenic carcinoma.

At operation adhesions were found between the upper lobe and the parietal pleura. On palpation an extremely hard mass was felt in the left upper lobe. The lesion was thought probably to be carcinoma and a left pneumonectomy was done.

The upper lobe was found to contain a hard, irregular mass measuring 6 by 6 by 5 cm. which extended to the pleura. No lesion was seen in the mucosa of the bronchus. The mass cut with resistance and was a mottled white and grey color.

Microscopic examination showed a typical paraffinoma which stained with Sudan III (Fig. 6).

Case 6. J. R. O., a 57 year old white man, entered Vanderbilt University Hospital Dec. 3, 1953 complaining of cough of six days duration and of hemoptysis of four days duration. It was said that he had coughed up as much as a pint of blood on one occasion. He had some temperature elevation but no chills. He had had dull, diffuse pain to the left of his sternum. There was no history of night sweats or tuberculosis contacts. He had taken mineral oil at night for many years as a laxative, but had not used nose drops.

Physical examination revealed a well developed, well nourished white man whose chest exhibited decreased breath sounds on the left posteriorly. The physical examination otherwise was not remarkable.

Roentgenologic findings revealed consolidation suggestive of atelectasis of the posterior apical segment of the left upper lobe with emphysema of the left lower lobe and anterior segment of the left upper lobe. The trachea and heart were displaced toward the left.

Bronchoscopy showed a great deal of fresh and old blood in the left bronchial tree. No tumor or bleeding point could be visualized.

Exfoliative cytology studies were negative.

At operation, the left upper lobe was found to be atelectatic and consolidated. The lesion appeared to be localized to that lobe and was not considered to be compatible with carcinoma. Left upper lobectomy was done.

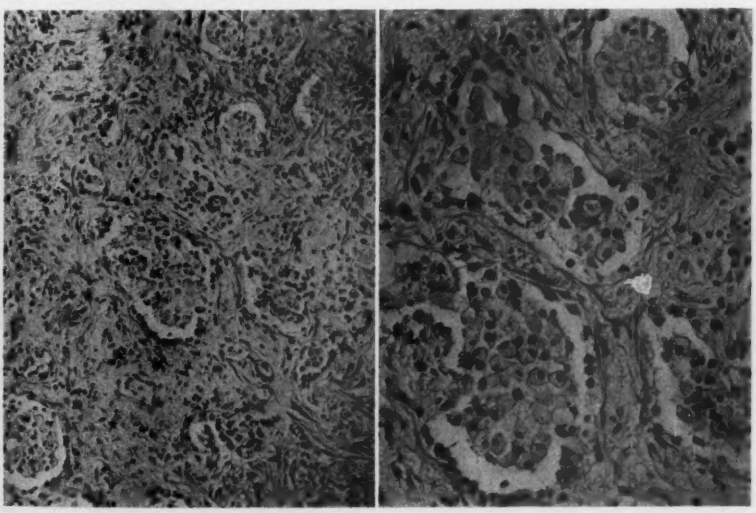

FIG. 6. Case 5. Photomicrographs which show marked fibrosis with scattered group of oil-filled macrophages.

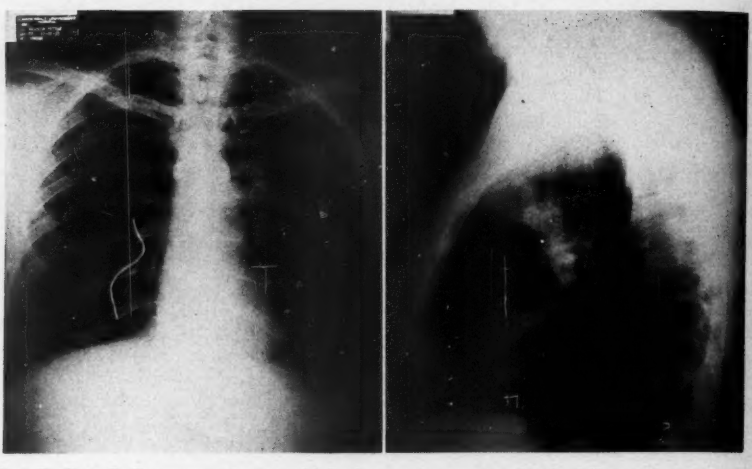

FIG. 7. Case 7. Roentgenograms which show a dense mass in the hilar region of the left lung.

Pathologic examination showed the posterior apical segment to be occupied by a firm, yellow-grey area of consolidation which was fairly well defined but not discrete. The entire apical and posterior segment of the lobe was hemorrhagic.

Microscopic examination revealed a typical paraffinoma which stained with Sudan III.

Case 7. M. S. P., a 36 year old white man, entered Vanderbilt University Hospital Dec. 22, 1953 complaining of pain in his chest and the coughing up of blood. Two years prior to admission he began to have a nagging, aching, squeezing pain in his chest just to the left of his sternum. The pain was most severe when recumbent, not related to exertion and remained the same intensity until two or three weeks prior to admission when it began to increase and he noted wheezing with respiration. Cough was productive of slightly blood streaked sputum. On the day prior to admission he suddenly coughed up a small quantity of bright red blood. He had taken mineral oil about three times weekly, always at bedtime, for three months prior to admission.

Physical examination revealed a large, well developed white man whose chest was clear to palpation, percussion and auscultation. There was no clubbing of the fingers.

Roentgenograms showed a wedge-shaped area of density extending from the hilus of the left lung into the anterior segment of the upper lobe which was thought to be atelectasis or pneumonitis (fig. 7).

Bronchoscopy and exfoliative cytology studies were essentially normal.

Impression was bronchogenic carcinoma or chronic lipoid pneumonitis.

At operation there was a very hard, nodular mass in the left upper lobe which extended from the visceral pleura downward in an irregular manner into the hilum of the lung. There were many enlarged lymph nodes in the superior mediastinum which were moderately firm and it was necessary to divide the phrenic nerve superior to them. Frozen section was obtained of one of these lymph nodes which showed only chronic inflammatory changes. The pulmonary artery was incorporated in the mass and a left pneumonectomy was done.

The specimen weighed 417 Gm. The hilar and apical portion of the lower lobe contained a nodular mass which extended upward into the upper lobe and within which were incorporated the major pulmonary vessels and bronchi. The hilar lymph nodes were enlarged, and were firmly fixed to the bronchi. One node was partially calcified and contained caseous material. Cut section of the lesion showed hard, grey, fibrous tissue and microscopic sections

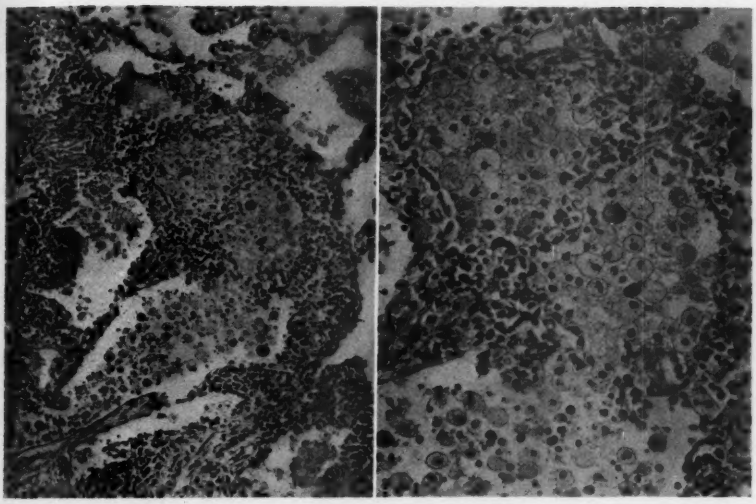

FIG. 8. Case 7. Photomicrographs which show marked thickening of the alveolar walls, leukocytic infiltration and an accumulation of giant macrophages which contain oil.

revealed a paraffinoma which was stained with Sudan III but not with osmic acid (fig. 8). Four and eight-tenths Gm. of mineral oil were extracted from the specimen.

DISCUSSION

We have encountered chronic sclerosing lipoid granulomas of the lung with increasing frequency during recent years. In 7 patients reported here the lesions were so much like carcinoma that pneumonectomy was done in 5. In all of these patients there was doubt as regards the question of the presence or absence of a malignant neoplasm. The inflammatory nature of the lesion was recognized at the time of operation in most patients, but in each instance it was thought likely that inflammatory changes had occurred concomitantly with or secondary to the growth of a neoplasm. The frequency of lung cancer and the importance of the avoidance of delay in radical definitive treatment have undoubtedly influenced us in these decisions.

Careful review of the symptomatology, the bronchoscopic and laboratory findings, the roentgenographic features and the gross evaluation of the lesions at operation have failed to reveal to us any clear-cut criteria which might distinguish the lipoid granuloma. In all of our patients surgical excision of the lesion was clearly indicated. However, the application of a radical surgical procedure, designed for the treatment of carcinoma, has led to the sacrifice of lobes which were essentially normal in a few patients.

In all of our patients a history of the repeated ingestion of mineral oil has been obtained. In only 2 patients was a history of the use of oily nasal medicaments obtained and both patients had also taken mineral oil by mouth at bedtime for several years.

In 1 case the patient had taken 1 or 2 oz. of mineral oil only twice weekly and for only three months prior to the onset of symptoms. He always had taken the oil at bedtime and this was true with all of our patients who used mineral oil as a laxative.

The importance of the knowledge of this habitual use of mineral oil only recently has become apparent to us, however, and was seriously considered in the differential diagnosis in only the last 3 cases reported here. Even then, the lesion could not be distinguished from carcinoma in 2 of the 3 patients.

Chronic cough, sputum production, hemoptysis, frequent or persistent respiratory infections, wheezing, dyspnea on exertion, anorexia and weight loss were all observed, in various combinations, by our patients. In some the symptoms were mild, in others severe and debilitating.

The roentgenographic appearance of the lesions has varied considerably and in most patients has been indistinguishable from carcinoma or chronic inflammatory disease such as chronic fibroid tuberculosis. Berg and Burford[1] have stated that the pulmonary paraffinoma appears as a homogenous shadow on the roentgenogram with sharply defined peripheral limits and a feathering of density at the hilar aspect. They point to the latter as a valuable diagnostic sign. The roentgenographic appearance of the lesions exhibited by our patients has not conformed to any pattern and we have been unable to point to any criteria which we believe are reliable in distinguishing this lesion as a clinical entity.

The statement repeatedly has been made by various authors, that this lesion can and should be distinguished at the time of operation by means of biopsy of the pulmonary tumor and of hilar lymph nodes and the examination of frozen sections. We believe that such a procedure is unwise. If carcinoma is exposed and identified in such a manner the chance of its complete extirpation certainly has been compromised and, in fact, probably lost entirely. It is our belief that the biopsy of cancer within the serous cavities, which otherwise might be curable, is dangerous because of the likelihood that it will result in the implantation of viable tumor cells in other parts of the cavity.

In 2 of the patients upon whom pneumonectomy was done, both with upper lobe lesions, an attempt first was made to perform lobectomy because of serious doubt as to the presence of carcinoma. In each case it became apparent that the mass extended into the hilum to the extent that the terminal portion of the pulmonary artery and its primary bronchus were incorporated in the tumor and that section through the tumor would be necessary to expose the upper lobe artery and bronchus at their origins. Therefore, radical pneumonectomy was done because it was thought that complete extirpation of the lesion could be accomplished in no other way.

It is our hope that, by placing more emphasis upon the history, the examination of the sputum and the gross characteristics of the tumor at operation, we may arrive at a more accurate means of diagnosis of this lesion. The presence of oil droplets—free or within monocytes—in the sputum will not of itself rule out the existence of carcinoma of the lung. The cancer-mimicking nature of the

pulmonary lipoid granuloma makes its recognition as the sole pathologic process extremely difficult at the time of operation. It appears at this time that the lesion may be encountered fairly frequently. The incidence of pulmonary carcinoma is much greater, however, and we are of the opinion that wherever the diagnosis cannot be established by careful study and the lesion is indistinguishable from carcinoma at exploratory operation, an attempt at complete extirpation is preferable to its piecemeal removal.

Aside from the confusion which may be occasioned by the difficulty in the differentiation of these tumors, lipoid granuloma of the lung itself may be a disabling disease. All of the patients whose cases are reported here were adults. None exhibited any subjective or objective evidences of neurologic deficit. All were actively engaged in useful occupations before the onset of symptoms which led to the discovery of their pulmonary lesions. In no case were symptoms elicited which suggested cardiospasm or abnormality in the swallowing mechanism. No cause was found for the debilitation noted in our patients other than their pulmonary lesions.

The inflammatory changes caused by the inhalation of petroleum products should be preventable. We believe that the use of mineral oil as a laxative, especially when taken shortly before sleep, often may be followed by its aspiration. Some publicity has been given to the dangers involved in the use of oily nasal applications and isotonic aqueous medications are advocated in their stead. Mineral oil is used widely as a laxative. We are of the opinion that wide publicity should be given to the serious sequelae which may ensue fron the habitual, and perhaps even from the occasional, use of mineral oil as a laxative and that particular emphasis should be placed upon the possible danger from its ingestion at the time of retiring.

SUMMARY

Seven cases with sclerosing lipoid granuloma of the lung are reported. This lesion has simulated carcinoma to such an extent that pneumonectomy was done in 5 cases.

The cause of the lesions is believed, in all cases reported here, to be due to the inhalation of mineral oil which had been taken with regularity as a laxative.

In all cases the patients were healthy, active adults prior to the onset of symptoms caused by the pulmonary lesions. In none was neurologic or developmental lesions, esophageal obstruction or derangements in the swallowing mechanism present.

The difficulty in the differential diagnosis of pulmonary lipoid granuloma and bronchogenic carcinoma is discussed.

The danger of the use of mineral oil as a laxative, especially when it is taken at bedtime, is emphasized.

The authors wish to express their appreciation to Dr. John Shapiro of the Department of Pathology and to Dr. Frank Blood of the Department of Biochemistry for their aid in this study.

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EXCISIONAL THERAPY FOR PULMONARY TUBERCULOSIS

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The excision of diseased pulmonary tissue in the treatment of tuberculosis has been done with increasing frequency during the past decade. During this period of time the mortality rate and the morbidity following excisional therapy have been greatly reduced. Factors which have contributed to the increasing safety of these surgical procedures include improvement in the preparation of the patient for operation; increase in technical skill, as experience has been gained; more accurate selection of the proper type of operation; adequate blood replacement during and after operation; increasingly better postoperative care and the protection afforded by antibiotics and chemotherapeutic agents.

It is generally recognized that pulmonary tuberculosis is a widespread disease and is seldom, if ever, confined to one lung. The proper aim of excisional therapy in the treatment of pulmonary tuberculosis is the removal of offending active lesions and not the removal of all tuberculous disease. The fact that tuberculous lesions remain in other portions of the lungs is of importance in the selection of the proper type of operative procedure for a given patient and also explains the necessity for relatively long periods of bed rest, the continued use of specific antibiotic and chemotherapeutic agents and a carefully controlled period of rehabilitation following operation. The patient must be given all possible help towards healing those lesions which are not excised.

This paper is concerned with 105 patients who were subjected to 112 consecutive operative procedures for pulmonary tuberculosis done during a four and one half year period, from 1948 to 1952. The ages of these patients varied between 19 and 71 years. There were 77 males and 28 females; 98 were white and 7 were Negroes.

The indications for operation and the number of operations done for each type of lesion are shown in table I. This table does not include all the possible indications for lobectomy or pneumonectomy in the treatment of pulmonary tuberculosis.

The types of operative procedures used are shown in table II. Lobectomy constituted almost two-thirds of the total number of operations, and pneumonectomy was considered to be indicated in only 16 instances. In 13 patients segmental lobectomy was done. Meticulous dissection of vessels and bronchi was employed in all segmental resections. Division along the intersegmental plane or planes was made by sharp and blunt dissection. Bleeding points and air leaks were controlled

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TABLE I

Resection for pulmonary tuberculosis

INDICATION FOR EXCISION	NUMBER OF OPERATIONS
1. RESIDUAL CASEOUS DISEASE	34
2. CHRONIC CAVITY (UPPER and MIDDLE LOBES)	22
3. THORACOPLASTY FAILURE	18
4. LOWER LOBE CAVITY	17
5. TUBERCULOMA	9
6. DESTROYED LUNG	4
7. BRONCHOSTENOSIS	3
8. TENSION CAVITY	3
9. BRONCHOPLEURAL FISTULA FOLLOWING RESECTION	2
TOTAL	112

by sutures and ligatures of fine silk. It is our opinion at the present time that segmental resection can be safely performed in a higher proportion of patients than is shown in this report. Wedge resection, in which relatively small portions of lung tissue were removed, was performed on 11 patients. More than one wedge resection was done in some instances on the same patient and in 1 patient three segments of lung tissue were removed from one lobe. No major complications resulted from the 11 wedge resections.

Seven of the 105 patients were subjected to two operative procedures. The types and location of the lesions necessitating the two operations are shown in table III. Pneumonectomy was completed at the second operation in 4 of the 7 patients and 2 patients died as the result of the second operation. The first of these (G. B.) was subjected to right upper lobectomy and resection of the superior segment of the right lower lobe because of the persistence of cavitation after thoracoplasty. Empyema and bronchopleural fistula resulted which were not controlled by a more extensive thoracoplasty and suture of the right upper lobe bronchial stump. Pneumonectomy was completed almost five months following the initial resection procedure and the patient died on the ninth postoperative

TABLE II

Resection for pulmonary tuberculosis

TYPE OF OPERATION	NUMBER OF OPERATIONS
LOBECTOMY	72
PNEUMONECTOMY	16
SEGMENTAL LOBECTOMY	13
WEDGE RESECTION	11
TOTAL	112

TABLE III

Resection for pulmonary tuberculosis

PATIENTS HAVING 2 RESECTIONS

V.A.H. PATIENT	INDICATIONS	OPERATION	COMPLICATIONS	RESULT
E.H. #8321	1) L L LOBE CAVITIES	LOBECTOMY, 4-28-49	NONE	GOOD, 1-5-53
	2) RESIDUAL CASEOUS DISEASE, LUL, WITH CAVITATION	LOBECTOMY, 6-7-51	NONE	
A.L. #27773	1) TENSION CAVITY, RUL	LOBECTOMY, 12-21-50	NONE	GOOD, 8-8-52
	2) RLL CAVITY (APEX)	LOBECTOMY, 2-28-52	NONE	
W.H. #11703	1) CHRONIC CAVITIES, LUL	WEDGE RESECT. (3) 6-1-51	NONE	GOOD, 12-1-52
	2) THORACOPLASTY FAILURE 1950	LOBECTOMY, 9-11-51	NONE	
G.B. #17726	1) THORACOPLASTY FAILURE 1950	LOBECTOMY, 3-30-51	B-P FISTULA	DEATH
	2) BRONCHOPLEURAL FISTULA	PNEUMONECT. 8-22-52	HEMORRHAGE	
V.E. #29484	1) RLL CAVITY	APICAL SEG. 10-3-51	B-P FISTULA	DEATH
	2) BRONCHOPLEURAL FISTULA	PNEUMONECT. 12-31-51	DEATH	
P.H. #33983	1) TENSION CAVITY, RUL	LOBECTOMY, 12-28-51	NONE	GOOD, 12-1-52
	2) CHRONIC CAVITY, LUL	APICO-POST. SEG. 5-1-52	NONE	
L.D. #30015	1) THORACOPLASTY FAILURE	LOBECTOMY, 6-19-51	NONE	GOOD, 12-1-52
	2) RESIDUAL CASEOUS DISEASE, RUL	POSTERIOR SEG. 10-8-52	NONE	

day of secondary hemorrhage from the pulmonary artery. The second patient (V. E.) developed empyema and a bronchopleural fistula following resection of the superior segment of the right lower lobe which contained a chronic cavity. Thoracoplasty was done which failed to close the fistula or obliterate the empyema space and the patient's general condition gradually worsened. Right pneumonectomy was done almost three months following the initial operation. The patient died a few hours after completion of the pneumonectomy. We believe that this patient's chance for survival would have been much better had pneumonectomy been done before his status became precarious.

A total of 7 patients died, this being an operative mortality rate of 6.25 per cent. Fifteen major complications resulted from the 112 operative procedures for

TABLE IV

Resection for pulmonary tuberculosis

COMPLICATIONS
112 OPERATIONS

TYPE	NUMBER	PERCENTAGE
BRONCHOPLEURAL FISTULA	4	3.5
TUBERCULOUS SPREAD	4	3.5
PULMONARY EMBOLUS	2	1.75
CLOTTED HEMOTHORAX	2	1.75
SECONDARY HEMORRHAGE	1	0.8
CONTRALATERAL PNEUMONIA, NOT TUBERCULOSIS	1	0.8
PULMONARY INSUFFICIENCY	1	0.8
TOTAL	15	13.4%

an operative complication rate of 13.4 per cent. The number and types of complications are shown in table IV. Four patients developed bronchopleural fistulas and 2 of these died. Four patients who had bronchogenic spread of the tuberculous process as the result of operation all responded well to treatment with streptomycin so that this complication did not cause the death of any patient and the final result in all was considered satisfactory. Fatal pulmonary embolus occurred once following pneumonectomy and once following lobectomy. The embolus was demonstrated at autopsy in each case. Operation was followed by massive clotted hemothorax in 2 patients and subsequent decortication of the lung resulted in satisfactory results in each of these. The one instance of hemorrhage from the pulmonary artery has been mentioned previously. One patient died on the fifth postoperative day of massive, contralateral, nontuberculous pneumonia and another died as a result of pulmonary insufficiency two days following right upper lobectomy done because of thoracoplasty failure. This last patient had scattered nodular disease throughout the remainder of the right lung and fibrotic changes in the upper left lobe. The right phrenic nerve was crushed following the lobectomy to help in obliteration of the pleural space. The causes of death are listed in table V.

It is our opinion that the over distention of lung tissue following excisional therapy has an adverse effect upon lesions which may be present in the remaining lung tissue even though these lesions appear to be stable or healed at the time of operation. Over distention of lung tissue may also result, eventually, in emphysema and diminished pulmonary function. We believe, furthermore, that a persistent pleural dead space may increase the incidence of empyema and bronchopleural fistula. It has been our practice, therefore, to do small apical thoracoplasty in many patients where upper lobectomy is done for tuberculosis. The thoracoplasty may be done before, at the time of, or following lobectomy. When thoracoplasty is done before lobectomy there is a tendency to decostalize too large a portion of the chest wall, and furthermore, the need for thoracoplasty cannot be

TABLE V

Resection for pulmonary tuberculosis

DEATHS 112 OPERATIONS		
CAUSE	NUMBER	
BRONCHOPLEURAL FISTULA	2	
PULMONARY EMBOLUS	2	
SECONDARY HEMORRHAGE, PULMONARY ARTERY	1	
CONTRALATERAL PNEUMONIA, NOT TUBERCULOUS	1	
PULMONARY INSUFFICIENCY	1	
TOTAL	7	%6.25

accurately determined until the time of lobectomy. If a fluid-filled apical pocket persists after lobectomy, there is at least some danger that pleural complications will develop before thoracoplasty is done. In either instance, the patient is subjected to the risk of an added operation. It is much better, we believe, to do the thoracoplasty at the time of lobectomy; to do so adds very little to the magnitude of operation; it permits a more accurate appraisal of the need for thoracoplasty and the extent of operation required to *tailor* the chest wall to the remaining lung; it provides for immediate obliteration of the pleural dead space and obviates the need for an added operative procedure. Apical thoracoplasty seldom is required following the removal of segments of the upper lobe. Figure 1 shows a roentgenogram of the chest of a patient with residual caseous disease in the right upper lobe. He was subjected to right upper lobectomy and a concomitant two and one-half rib thoracoplasty. Figure 2 shows the patient's chest roentgenogram four months following operation. There is little deformity present and there is no evidence of over distention of the remaining right lung.

We no longer crush the phrenic nerve as a means of filling pleural dead space postoperatively. The loss of pulmonary function following interruption of the phrenic nerve and the loss of the use of the diaphragm with resulting ineffective cough is undesirable. The latter is especially undesirable in the early postoperative period when it is imperative that the tracheobronchial tree be kept free from secretions. An existing therapeutic pneumoperitoneum can be used as a safe and effective means of obliterating remaining pleural space, particularly after lower lobectomy. We do not advocate thoracoplasty following removal of the lower lobe. The pleural space usually is obliterated quickly and completely when the upper lobe is left in place.

Over distention of the contralateral lung following pneumonectomy for tuberculosis may become extreme in degree. In addition, a large pleural space is left which invites infection, either with or without bronchopleural fistula. One of our patients became ill from tuberculous empyema four years following pneumonectomy, after having been in apparent good health during the interim. We think that it is desirable that the pleural space be obliterated quickly following pneumonectomy for tuberculosis. To accomplish this we now often do preliminary thoracoplasty, removing all of the first two ribs and shorter posterolateral segments of the third and fourth ribs. Approximately two weeks later pneumonectomy is done and the thoracoplasty is extended as is necessary to produce the desired degree of collapse. The phrenic nerve may be interrupted to lessen the extent of thoracoplasty required. Usually the collapse need not be carried below the eighth rib. Drainage of the pleural cavity is provided during the first few postoperative days to allow immediate collapse of the decostalized chest wall. Figure 3 shows the chest roentgenogram of a patient with a destroyed left lung. A preliminary three and one-half rib thoracoplasty was done, followed two weeks later by pneumonectomy and completion of the thoracoplasty. Figure 4 is a chest roentgenogram of this patient five months following the second operation. The degree of collapse appears to be adequate and deformity of the spine, which is

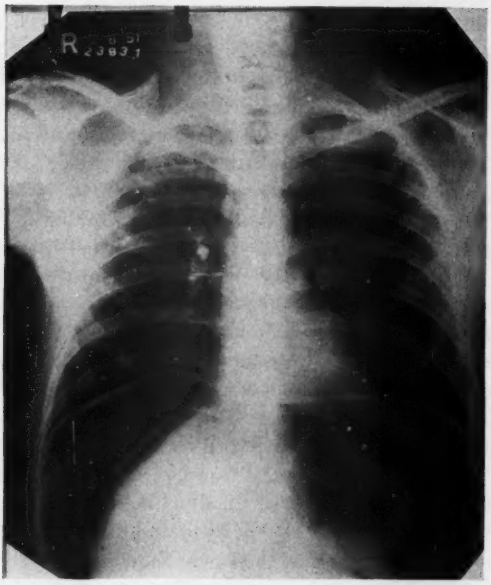

FIG. 1. Residual caseous disease, right upper lobe. Preoperative roentgenogram

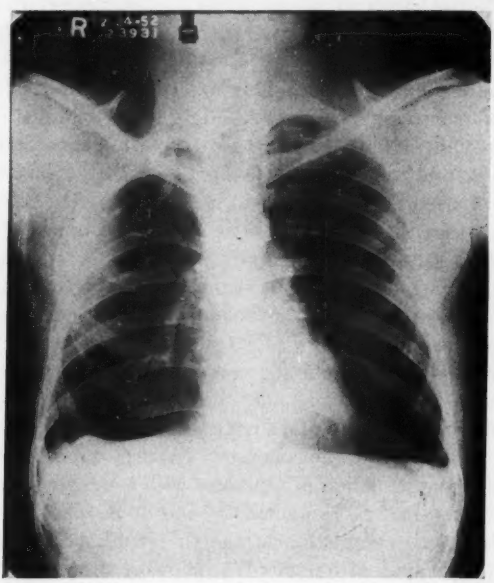

FIG. 2. Postoperative roentgenogram four months following upper lobectomy and small apical thoracoplasty.

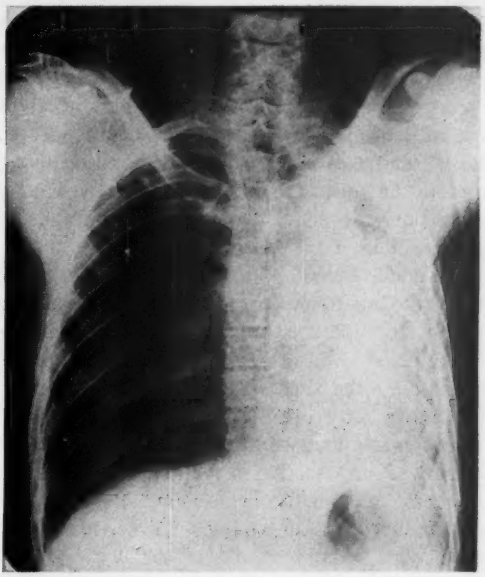

FIG. 3. Postoperative roentgenogram of patient with destroyed left lung

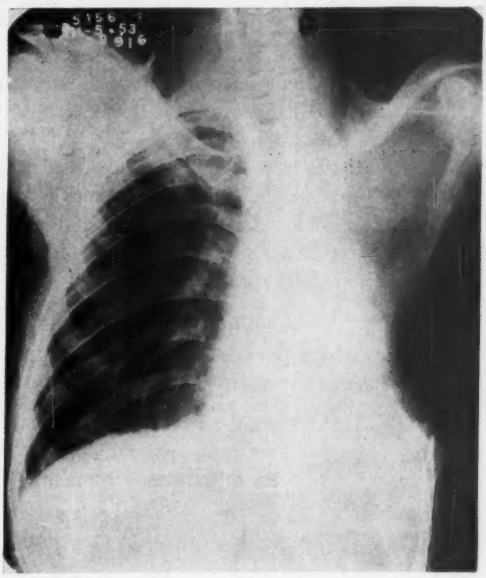

FIG. 4. Roentgenogram made five months after left pneumonectomy and thoracoplasty

limited by the presence of relatively long posterior rib stumps, is not great. There is no shift of the mediastinum to the side of operation and there is no evidence of emphysematous changes in the right lung.

In general, the preoperative preparation of these patients included prolonged bed rest with adjunctive antibiotic and chemotherapeutic agents and the correction of nutritional deficiencies. The control of any existing secondary infection, with the reduction of sputum output to a minimum, has received particular attention. Therapeutic pneumoperitoneum was used rather frequently, particularly in patients with lower lobe and bilateral disease.

Operation was done under general anesthesia, often with cyclopropane induction, and with ether as the maintenance agent in almost all instances. Anesthesia was maintained with cyclopropane in only a few of the operations. The patients were carried in a light plane of anesthesia and in the majority of cases had regained the cough reflex by the time the operative procedure was completed. Bronchoscopy immediately after operation was rarely necessary. The patients were encouraged to cough frequently and vigorously during the first few postoperative days. If cough was not effective in maintaining a clear tracheobronchial airway, tracheal catheter suction, bronchoscopy, and even in rare instances, tracheostomy, were employed. In our experience it has not been necessary to do bronchoscopy frequently.

The pleural cavity was entered through a posterolateral approach with the patient in the lateral decubitus position in the majority of the operations. The prone position was used almost exclusively for lower lobectomy and occasionally for upper lobe disease when sputum production was relatively large. The posterolateral approach has the advantage of affording ready access to all portions of the pleural cavity and allows the surgeon great freedom in the accurate dissection of any portion of the lung. We believe it is significant that contralateral tuberculous spread has occurred in only 4 patients in this series.

Following operation the patients were kept at bed rest for at least six months and continued to receive adjunctive antibiotic and chemotherapeutic agents for variable periods of time. After six months of postoperative bed rest the activity schedule was gradually increased in accordance with accepted conservative principles of rehabilitation in tuberculous patients.

RESULTS

These patients were followed for periods of time varying from six months to five years. The present status of the patients is shown in table VI. A satisfactory

TABLE VI

The results following operation upon 105 patients

	NO. OF PATIENTS	PER CENT
SATISFACTORY	87	82.9 %
IMPROVED	3	2.8 %
UNIMPROVED	3	2.8 %
DEAD	8	7.6 %
UNKNOWN	4	3.8 %

result denotes that the sputum was persistently negative and that there was no other evidence of active tuberculous disease. Those patients who are classed as improved exhibited no symptoms or roentgenographic evidence of active tuberculous infection, but a few tubercle bacilli occasionally were demonstrated by smear or culture. The 3 patients listed as unimproved had extensive bilateral disease and their status was not essentially changed following the operative procedure.

SUMMARY

Our experience in the excisional therapy of pulmonary tuberculosis has been reviewed. One hundred and twelve operative procedures performed upon 105 consecutive patients are reported.

Seven patients died as a result of operation, an operative mortality rate of 6.25 per cent.

There were postoperative complications of serious importance in 15 instances, or 13.4% of the total cases done.

The authors' opinions concerning the possible dangers of residual pleural cavities and the need for thoracoplasty following pneumonectomy and upper lobectomy are discussed.

The follow-up data on this group of patients are tabulated.

CONCLUSIONS

Excisional therapy for pulmonary tuberculosis can be accomplished safely in carefully selected patients.

Complications, when they do occur, are usually more catastrophic than those which follow surgical collapse measures for tuberculosis, particularly extrapleural thoracoplasty, or excisional therapy for nontuberculous lesions.

It is our opinion that the obliteration of pleural dead space is a factor of importance in the avoidance of complications and thoracoplasty is, therefore, indicated in patients who are subjected to pneumonectomy for tuberculosis as well as in certain patients in whom upper lobectomy is done.

THE TECHNIC OF VAGUS NERVE RESECTION

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Vagotomy combined with gastric resection of varying extent or coupled with gastroenterostomy appears at the present time to occupy a definite place among the recognized procedures composing the armamentarium of the gastric surgeon.

There seems to be at present more interest and enthusiasm in regard to vagotomy than has existed in the recent past. This is attributable in great part to a better understanding of the reasons for the earlier reported failures. Also, the good results utilizing vagotomy have, to some extent, remained unheralded, as it is usually the tendency with any new procedure to place emphasis particularly on the failures.

Of the poor results recorded in the literature some have comprised cases in which the procedure was performed transthoracically, with gastric atony constituting a troublesome complication. In patients with gastric ulcer receiving vagotomy, the over-all results have been poor and the procedure has been abandoned as a means of treating gastric ulcer except in certain selected cases. Pyloroplasty coupled with gastroenterostomy has been somewhat ineffectual in preventing gastric stasis and only recently has proper emphasis been placed on posterior, greater curvature gastroenterostomy[6] in alleviating this problem. With a better understanding of gastric physiology and the immediate postoperative care of the vagotomized patient, the errors in the recent past are being corrected. Possibly the largest number of reported failures have resulted from incomplete interruption of the vagal pathway.

There can be no doubt that, in order for vagotomy to accomplish its usefulness, the denervation of the stomach must be complete. If one studies the patterns of the distribution of the vagi in the region of the esophageal hiatus,[1, 7] it is readily understandable that, unless a thorough and systematic search is conducted, intact vagal fibers may be overlooked. In no other abdominal operation are the requisites of proper exposure, adequate lighting, good anesthesia, able assistants and a meticulous dissection more conducive to a good result.

The accepted technics utilizing vagotomy employ the same basic principles with minor differences, depending upon the individual operator. Crile[3] does not deem it necessary to divide the left triangular ligament to gain adequate exposure and does not mobilize the esophagus. Jackson[5] prefers to do a selective vagotomy by dividing the anterior vagal trunk and only the gastric branches of the posterior trunk, thus leaving the celiac division intact. He believes that the stomach thereby is denervated of its parasympathetic supply, and the innervation of the

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adjacent viscera is preserved. Some authors rightly have stressed the importance of accessory nerve fibers in addition to the two main trunks,[4] while others mention only a right and a left vagus nerve at the diaphragmatic level.[8]

The purpose here is to describe a technic of transabdominal vagotomy, which in our opinion, if properly done, provides the operator with the satisfaction and assurance that as complete a denervation as possible has been done. The operation, in the main, closely parallels the ones generally accepted, with certain modifications.

TECHNIC

First, the type of abdominal incision is of utmost importance. Early in our experience we found that a transverse or oblique incision in the upper abdomen gave poor access to the gastroesophageal region. The exposure, which has proved most useful, is a modification of that described by Cole[2] and is accomplished through a long left paramedian incision beginning at the costal arch to the left of the ensiform cartilage, and extending inferiorly to a point 1 to 2 centimeters above the umbilicus. At this level the incision is curved to the right for approximately 10 centimeters dividing the right rectus muscle (fig. 1). It is important that the vertical component of the incision commence just inferior to the costal arch, as the esophagus lies in approximately the same vertical plane. The horizontal component provides for an increased exposure over that obtained with the standard vertical incision, thus facilitating the procedure and enabling the assistants to exert very little effort with retractors. One is impressed with the exposure obtained in carrying out a difficult duodenal stump closure. The same incision has proved of value in doing pancreatic surgery and total gastrectomy. A similar incision, but with the horizontal component directed to the left, is useful in doing a splenectomy.

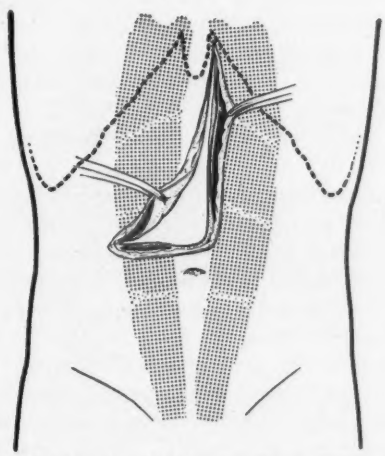

FIG. 1. Modification of incision described by Dr. Warren Cole which allows excellent exposure of the esophageal region and is of inestimable value in doing gastric resection.

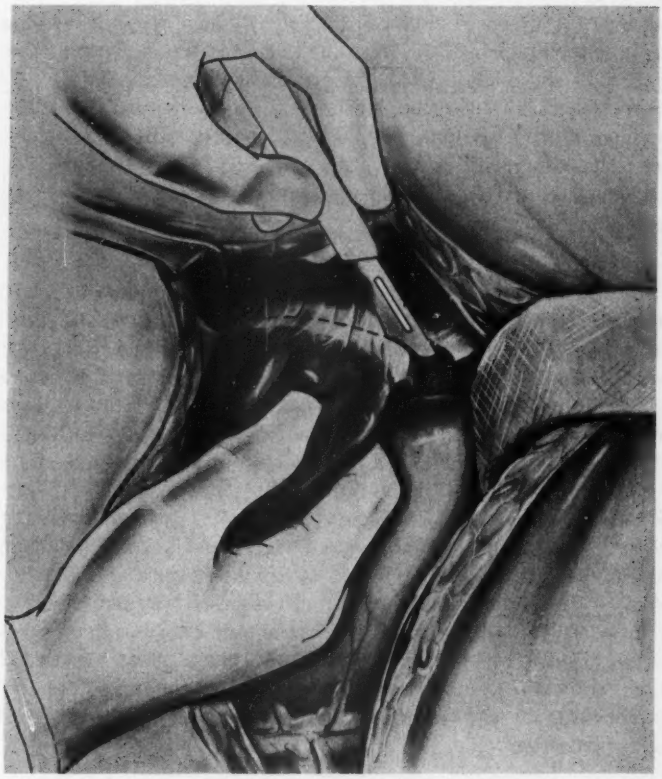

FIG. 2. Triangular ligament of the left lobe of the liver being divided by the operator.

Upon opening the abdomen, a thorough exploration of the abdominal viscera is made. The extent of the duodenal ulcer is established, including its relationship to the pancreas and common bile duct. One is then ready to proceed with vagotomy.

The left lobe of the liver is gently grasped with the thumb and fingers of the right hand and gentle downward traction is made. The left triangular ligament is thus rendered taut, and with the knife in the operator's left hand, the ligament is divided—care being taken not to divide the ligament close to its liver attachment—or troublesome bleeding will ensue (fig. 2). This maneuver frees the left lobe to a great extent, enabling the operator to displace the lobe to the right while an assistant maintains it in the desired position with a stockinette covered Deaver retractor. The left leaf of the diaphragm and lower esophageal area with its peritoneal covering then are brought into view. A moist pack next is placed in the left upper abdominal quadrant to protect the spleen and a moist pack is likewise used to cover the stomach. Assistants with two stockinette covered Deaver re-

tractors placed in the upper portion of the wound exert gentle traction and provide an excellent exposure of the operative field.

The peritoneum overlying the esophagus is gently elevated with long forceps and incised horizontally for a distance of 3 to 4 centimeters. Care should be taken that the incision in the peritoneum be placed just inferior to the margin of the diaphragm, never low, near the esophagogastric junction. The right index finger next is inserted into the peritoneal rent and advanced around the left lateral wall of the isophagus. With gently blunt dissection the finger progresses posteriorly and around the right lateral wall until it emerges anteriorly through the original peritoneal incision, thus completely encircling the esophagus. Rather dense fibrous tissue may be encountered during this maneuver, but with care and the use of a Levine tube in the esophagus as a guide, injury to this hollow viscus is readily avoided. The isolation of the esophagus greatly facilitates the subsequent steps.

The esophagus now may be gently retracted downward for a distance of 4 to 5 centimeters. The right vagus nerve, usually the larger of the two, is exposed with the right thumb and index finger. The nerve usually may be found in one of four locations: (1) on the posterior wall of the esophagus in contact with the longitudinal musculature, (2) embedded in the areolar tissue between the esophagus and

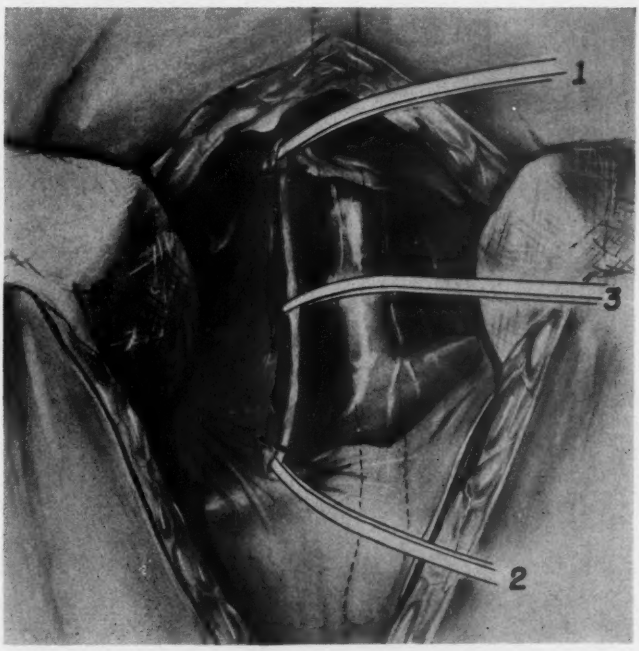

FIG. 3. Right vagus nerve has been mobilized and broken lines indicate length of the segment to be excised.

the aorta, (3) along the anterior wall of the aorta, (4) to the right of the esophagus, a distance of 1 to 2 centimeters, embedded in periesophageal fibrous tissue. Once located, the nerve has the feel of a taut violin string and readily is distinguishable from tough strands of fibrous tissue. When the nerve is brought into view by the operator, an assistant slides a long curved clamp along the course of the nerve freeing it completely from any adherent fibrous tissue. The clamp then is slid along the nerve proximally, as high as the esophageal hiatus, and the jaws closed. A second clamp then is placed on the nerve about 2½ to 3 inches distal to the first one. A third clamp is placed midway between clamps number one and two (fig. 3). An assistant then divides the nerve between the latter two clamps. The specimen is readily lifted out with clamps number three and sent to the laboratory for confirmation of the presence of nerve tissue. Each divided end of the nerve is tied with a silk ligature because a small blood vessel may be present in the tissue. The proximal cut end of the nerve readily retracts into the posterior mediastinum.

The left vagus nerve usually is smaller and may be found anteriorly embedded in the longitudinal musculature of the esophageal wall (fig. 4) or in the loose tissue to the left of the esophagus. It is dealt with in essentially the same manner as that described for the right nerve.

To terminate the dissection at this point may invite disaster. In our experience

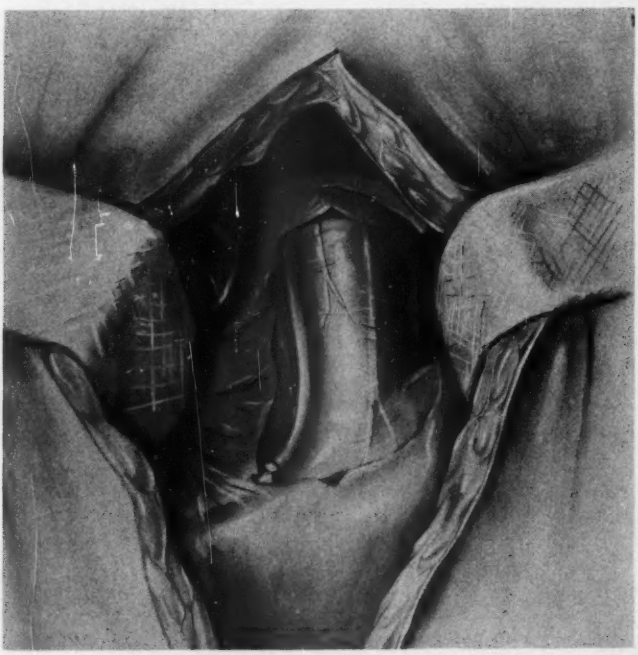

FIG. 4. Usual location of the left vagal trunk. A small accessory fiber is also visualized.

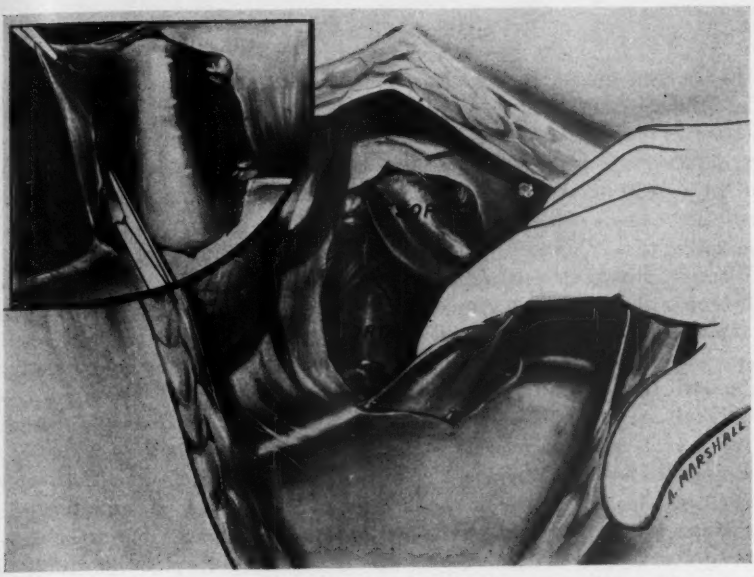

FIG. 5. Entire operative area is thoroughly *skeletonized* to remove all possible nerve filaments.

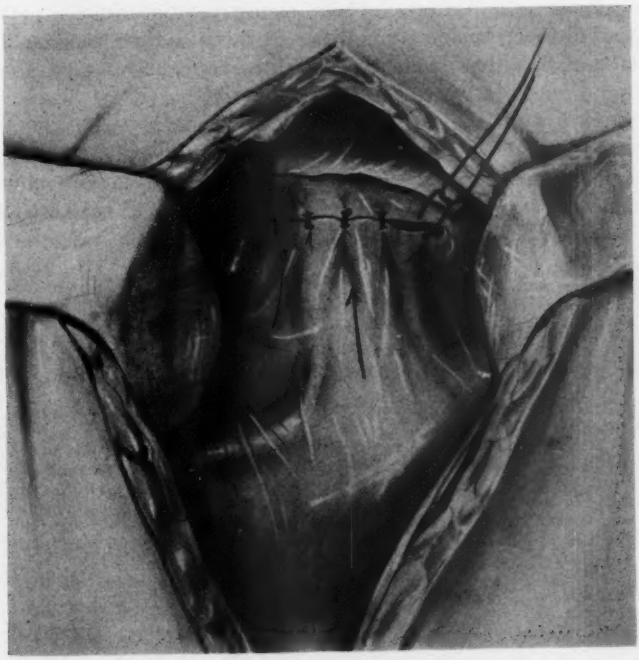

FIG. 6. Region reperitonized at completion of procedure with interrupted fine silk sutures.

it has not been unusual to find a third fairly large nerve trunk to the left—splenic side—of the esophagus in a posterior plane and embedded in fibrous tissue. Also one or two macroscopic fibers may be detected in the areolar tissue about the anterior esophageal wall, sometimes embedded in the musculature of the esophagus. In a small number of patients we have removed as many as three macroscopic nerve fibers in addition to the main trunks. A nerve hook is advantageous in isolating these filaments.

When all grossly demonstrable fibers have been dealt with, the areolar tissue adherent to the esophageal musculature next is removed along the entire length of the exposed esophagus and around its circumference. The fibrous tissue between the esophagus and the aorta is stripped so that the anterior wall of the latter structure is clearly demonstrated. The diaphragmatic crura stand out plainly following this dissection. All areolar tissue extending from either side wall of the esophagus laterally for a distance of 2 to 3 centimeters is removed (fig. 5). One is impressed by the frequency with which the pathologist reports microscopic nerve filaments present in the removed tissues. A final inspection of the entire area is made, after which the peritoneum overlying the lower esophagus is approximated to the margin of the diaphragm with interrupted silk sutures (fig. 6). The left lobe of the liver is allowed to return to its normal position, no attempt being made to suture the triangular ligament.

Either gastroenterostomy or a subtotal gastric resection is added to the vagotomy, depending upon the operator's choice. So far in our experience an estimated 40 per cent resection, thus eliminating the antral segment, has given best results.

SUMMARY

A brief description of the technic of vagus resection has been presented. Emphasis has been placed upon the importance of complete exposure and isolation of the esophagus and excision of all fibrous and areolar tissue throughout the limits of the operative field, in addition to the removal of all macroscopic nerve trunks.

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SURGERY OF CONGENITAL BILIARY ATRESIA

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There have been an increasing number of scattered surgical successes in congenital biliary atresia during the past decade. Holmes[2] in 1916 stated that theoretically, 16 per cent should be cured. Recently, Norris and Rothman[4] have raised this figure to between 50 and 60 per cent. Gross,[1] however, found that only 27 of 146 patients (18 per cent) operated upon for congenital biliary atresia had some condition which could be remedied by anastomosis. He did report an overall salvage rate of 22 per cent.

There is complete agreement that all of these jaundiced babies should be explored sometime within the first three months of life or as soon as icterus neonatorum, erythroblastosis fetalis, syphilis, sepsis, virus hepatitis and obstruction due to inspissated bile or mucus can be excluded.

Judging from recent case reports, there is a tendency toward earlier exploration and the performance of varied procedures. Hepaticoduodenostomy over a short segment of ureteral catheter is the method advocated by Gross[1] when possible. McCarry and Pence[3] reported a case of a patient in whom they created a fistula between the right lobe of the liver, the gallbladder and the duodenum. There was complete atresia of the hepatic ducts in their patient. The anterior wall of the gallbladder was incised and a deep stab wound made into the liver with a scalpel. An anastomosis was then made between the gallbladder and duodenum. Bile stained stools were noted on the third postoperative day. The child had repeated bouts of fever, jaundice and enlargement of the right lobe of the liver. At 8 months of age, the pylorus was closed and a gastrojejunostomy was done. The child died 48 hours later from bile peritonitis due to disruption of the duodenal closure. Autopsy showed several bile ducts that emptied into the sinus tract which extended into the right lobe of the liver. This procedure was done on 2 dogs, along with ligation of the cystic and common bile ducts. The first dog died of hemorrhage in 24 hours and the second died one week after operation from perforation of the fundus of the gallbladder and bile peritonitis.

Strauss[5] found one-third of his patients to be amenable to surgery. He established a preliminary biliary fistula by inserting a small catheter into the hilum of the liver near the obliterated hepatic ducts and later using a special vitallium tube with a Roux-en-Y procedure.

The result in the patient whose case is to be reported in detail shows that some procedure on or near the hepatic ducts occasionally may be successful even though patency of the ducts cannot be demonstrated.

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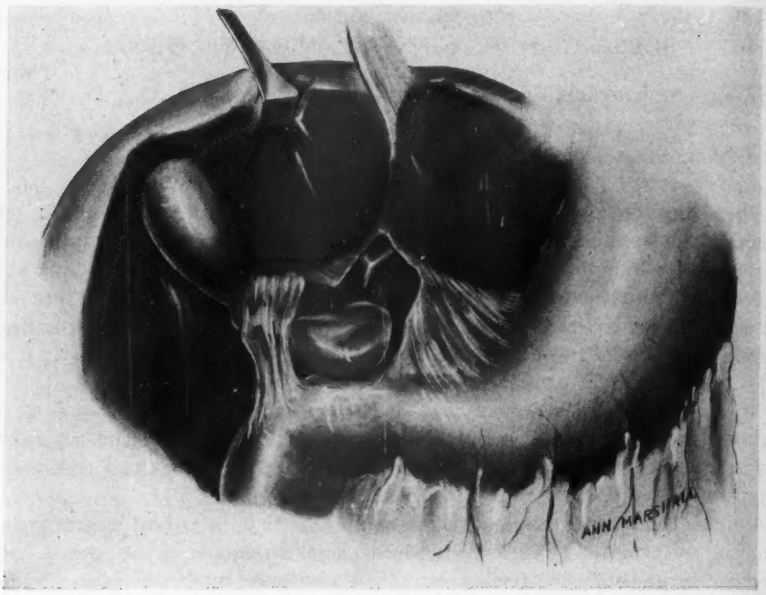

FIG. 1. Artist's conception of atretic ducts and dilated gallbladder and choledochus cyst which did not communicate with either the hepatic ducts or the duodenum.

CASE REPORT

M. A. R., Vanderbilt University Hospital, a white female was delivered normally on Oct. 29, 1950, weighing 7 pounds and 8 ounces. The stools were noted to be paler and the urine darker than normal. There was progressive jaundice and an increase in the size of the liver. She was admitted to Vanderbilt University Hospital Jan. 3, 1951. Serum bilirubin was 9.4 mg. per cent; alkaline phosphatase was 18.6 Bodansky units and the bleeding time was 8 minutes.

An exploratory operation was done on January 9, at 2½ months of age. The gallbladder was slightly distended with a clear, mucoid material. The cystic duct extended down to a dilated pouch which did not communicate with the duodenum. Tiny cords were found at the porta of the liver which apparently represented the hepatic ducts (fig. 1). The cyst and gallbladder were explored and partially excised. The fibrous cords were injected and incised but no definite lumen could be seen. A portion of these cords was excised for microscopic examination and was found later to have a tiny channel which could not be identified as a bile passageway. It was believed that complete atresia of the hepatic ducts existed and a cigarette drain was placed down to the hilum of the liver because of the dissection of the gallbladder and cyst of the common duct (fig. 2).

To our surprise bile drainage appeared within 48 hours. The serum bilirubin fell to 5.2 mg. per cent on the tenth postoperative day and the patient was discharged with a fistula draining bile. The patient did fairly well at first, but began to refuse food and on February 16, had tonic spasms thought to be tetany. She was readmitted to Vanderbilt University Hospital. Unfortunately an inadequate amount of blood for both calcium and phosphorus was drawn but a blood phosphorus level of 6.4 mg. per cent strongly suggested a low calcium level. Tonic and clonic seizures were controlled by calcium gluconate and calcium lactate. It was thought that the loss of bile and base through the biliary fistula caused the

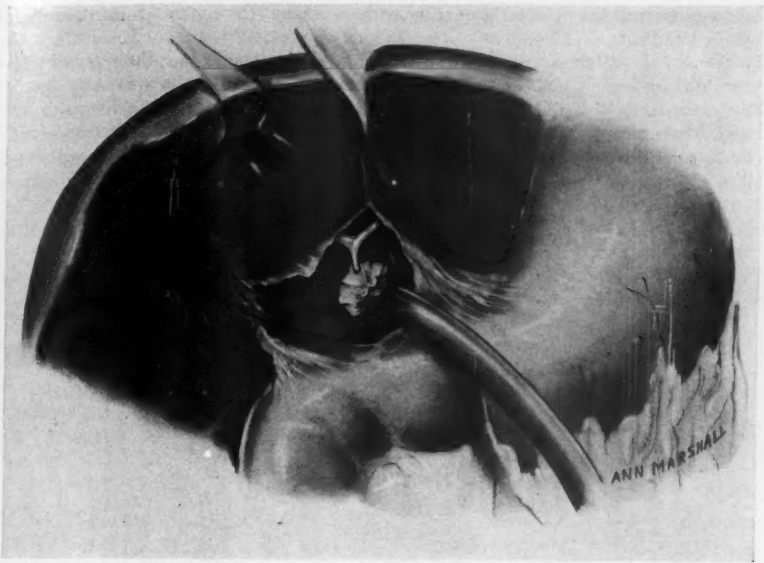

FIG. 2. Cigarette drain placed near hilum although patency of hepatic ducts could not be demonstrated.

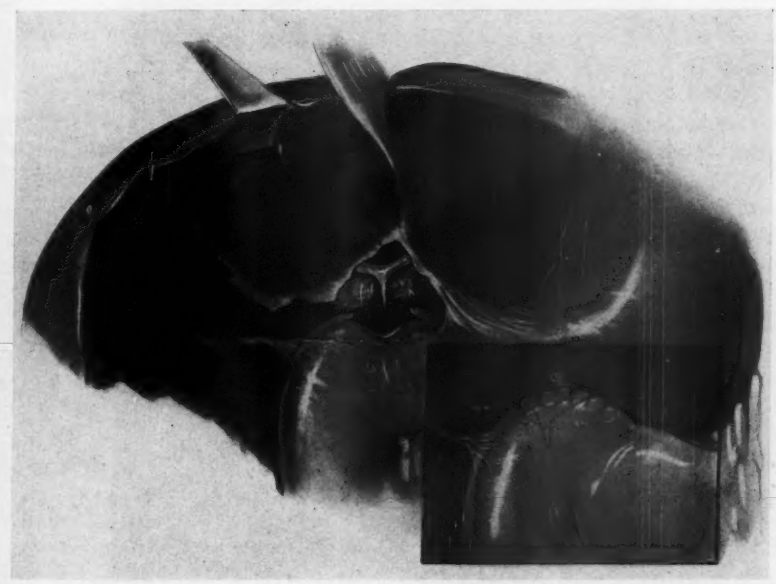

FIG. 3. Opening in duodenum placed over the partially patent ducts at second operation six weeks later.

chronic tetany and that an effort should be made to convert the external biliary fistula into an internal fistula.

The second operation was done on February 23. It was thought that the external biliary fistula might be dissected out and inserted into the duodenum, but the wall of the fistulous tract was made up of loops of duodenum and jejunum. The hilum of the liver was again exposed. There was no dilatation of the small fibrous cord which had been transected at the first operation but a drop or two of bile was seen to exude from it. The cord was too small to anastomose directly to the intestine so the adjacent duodenum was brought up and one row of sutures placed inferiorly in relation to the hepatic duct. An opening was then made in the duodenum and a superior row of sutures was placed between the duodenum

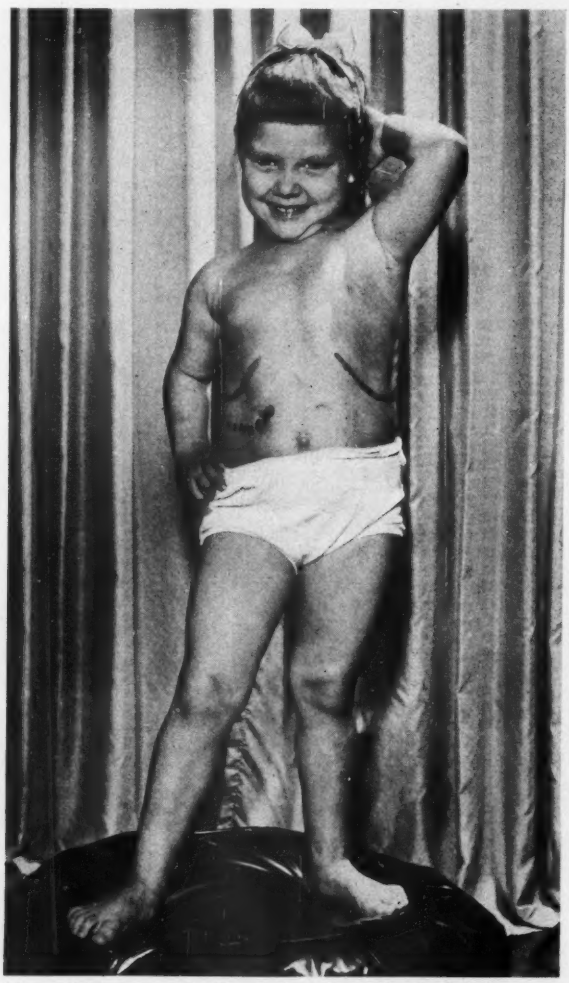

FIG. 4. Child now 3½ years old. Liver edge shown by dotted line, costal margin by solid line.

and the fibrous tissue around the hilum so that the hepatic duct was encompassed by the opening in the duodenum. There was ample tissue at this time for suturing the duodenum over this tiny duct which was not present at the first operation (fig. 3).

Three days later the stools were bile stained and the serum bilirubin was less than half the preoperative value. Convalescence was uneventful. The child was readmitted to Vanderbilt University Hospital on May 29, 1952, for evaluation of liver function tests. The liver edge was palpated 3 fingerbreadths below the costal margin. The stools were normal in color and the following laboratory tests were reported:

Hemoglobin—12.1 Gm.

Urine—normal

Prothrombin time—100 per cent

Total serum protein 6.58 Gm. per cent; Albumin—4.63 Gm. per cent; Globulin—1.95 Gm. per cent.

Serum bilirubin—direct 0.3 mg. per cent; indirect—0.3 mg. per cent

Thymol turbidity—1.5 Maclagen units

Cephalin flocculation—negative at 24 and 48 hours

More recent check-up examinations have shown a well developed and well nourished child who has had no jaundice, fever or symptoms relative to her biliary system (fig. 4). At the present time the liver edge is felt about 3 cm. below the costal margin.

COMMENT

This patient fortunately did not have complete atresia of the hepatic ducts, although this could not be determined at the time of operation and microscopically no bile passageway was seen. There was no apparent dilatation of the duct during the six weeks in which there was an external biliary fistula. The formation of fibrous tissue about the drain and hilum of the liver during this period made the hepatoduodenal anastomosis technically easy and secure. The absence of complications and the normal development of this child suggest that this procedure might be tried in either one or two stages in those patients in whom neither the gallbladder nor the common duct can be anastomosed to the intestine. It obviously will not be successful in complete atresia of the hepatic ducts, but partial patency may occasionally exist that cannot be determined at the time of exploration.

During the past 12 years (1942–1953) the clinical diagnosis of biliary atresia has been made in 12 patients at Vanderbilt University Hospital. Nine of these infants had abdominal exploration. The diagnosis was confirmed at autopsy in 2 infants and the parents of the remaining child refused any surgical procedure. One, of the 9 patients who were explored, proved to have inspissated bile and made a complete recovery. In only 1 infant, the case report cited, was a successful anastomosis accomplished. In the remaining patients the hepatic ducts were thought to be atretic and not amenable to any surgical intervention.

In the patient reviewed in this report, it should be emphasized that patency of the hepatic ducts could not be determined either grossly or microscopically at the time of exploration. The artist's conception (fig. 1) is somewhat misleading as to the actual size of the ducts which were smaller than those in the illustration. Our experience shows the value of extensive dissection around the hilum of the liver with division of all cord-like structures and the provision of drainage either to the outside or into the intestinal tract.

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WILMS'S TUMOR

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This is a report on 18 cases of Wilms's tumor, proved by pathologic sections, seen in Vanderbilt University Hospital from 1925 through March 1950. The symptoms, physical findings and metastases have been amply reviewed in previous papers by Garrett,[1] Rusche[2] and many others. It is our purpose to add to the literature 18 cases of Wilms's tumor which have been treated for all intents and purposes in an identical manner. In this series there were 13 males and 5 females.

TABLE I

Case No.	Hosp. No.	Sex	Age	Treatment		Length of Survival
				Surgery	Post-operative radiation therapy	
1	176650	M	10 wk.	Transperitoneal nephrectomy	Yes	Living 5 years
2	175987	M	8 mo.	Kidney incision nephrectomy	Yes	Living 5 years
3	181610	M	9 mo.	Transperitoneal nephrectomy	Yes	Living 4½ years
4	168394	M	13 mo.	Transperitoneal nephrectomy	Yes	Deceased 6½ months
5	161228	M	16 mo.	Transperitoneal nephrectomy	Yes	Deceased 7½ months
6	127049	M	18 mo.	Transperitoneal nephrectomy	Yes	Living 11 years
7	153036	M	20 mo.	Transperitoneal nephrectomy	Yes	Living 7½ years
8	175828	F	2 yr.	Transperitoneal nephrectomy	Yes	Deceased 13 months
9	186160	M	2 yr.	Kidney incision nephrectomy	Yes	Living 4 years
10	20009	F	2½ yr.	Transperitoneal nephrectomy	Yes	Deceased 1 year
11	101834	F	3 yr.	Transperitoneal nephrectomy	Yes	Deceased 3½ months
12	27098	F	3 yr.	Kidney incision nephrectomy	Yes	Deceased 11 months
13	76337	F	3 yr.	Transperitoneal nephrectomy	Yes	Deceased 5 days
14	143376	F	3 yr.	Transperitoneal nephrectomy	Yes	Deceased 1 year
15	149220	M	4 yr.	Transperitoneal nephrectomy	Yes	Deceased 9 months
16	106188	F	4 yr.	Transperitoneal biopsy		Deceased on table
17	143517	M	1 yr.	Transperitoneal nephrectomy	Yes	Living 8 years
18	108321	M	2 yr.	Transperitoneal nephrectomy	Yes	Deceased 2 months

Of the 18 patients, 7 are still alive from 4 years to 11 years, 11 patients having died within the first year and 1 during the second year after operation. The best results were obtained in the younger age group as has been noted in other reports. We were unable to predict the outcome of any of these patients from either the pathologic sections, history, or the length of time between the diagnosis and the operation.

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All patients except 1 were treated by nephrectomy; 14 operations having been done by the transperitoneal method; three by the flank incision extraperitoneally and in 1 only a biopsy section was done by the transperitoneal approach. None of the patients had preoperative radiation therapy. All of them had postoperative radiation therapy except 1 who died on the operating table (table I).

COMMENT

The period of follow-up of only four years, rather than the type of treatment, conceivably could account for our relatively high survival rate. If there is no evidence of recurrence or metastasis within 24 months after operation, it is highly probable that a permanent cure has been obtained. Although none of our patients had preoperative radiation therapy, it may be that it should be given if the Wilms's tumor is unusually large. It is possible that, in an effort to expose the kidney pedicle in a very large tumor, the consequences of the manipulation may be more serious than the delay of the operation for preoperative radiation. In our opinion, each case should be individually assessed and not necessarily treated as an emergency.

SUMMARY

Eighteen microscopically proved cases of Wilms's tumor have been reported with 7 patients surviving over four years, a survival rate of 38.8 per cent.

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MUCINOUS ADENOCARCINOMA OF THE URACHUS

REPORT OF A CASE

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The development of the embryo in the mother, as concerns the umbilicus, is a fairly complex process relating to nutrition of the child as well as the development of the intestine and excretory organs. As all mammals must have an umbilicus, so do they all have a urachus. Despite the constant presence of this structure, the occurrence of carcinoma in the urachus is extremely rare. In 1931, Begg[1] could find only 19 recorded instances since 1863. The world literature subsequently was well reviewed in 1945 by Hayes and Segal[5] to reveal 44 cases. In 1953, Slater and Torassa[7] reviewed the entire literature and presented a case. Counting their case, the total number of mucinous adenocarcinomas of the urachus was 60. To this must be added 2 cases reported in 1952 by Carreau and Higgins,[3] one by Orr and Hardin,[6] and one by Bobrow,[2] to bring the total in the world literature to 64. Hence, this apparently is the sixty-fifth reported case of carcinoma of the urachus. Therefore, one must conclude that, despite the omnipresent umbilicus and urachus, this highly fatal mucinous adenocarcinoma of the urachus is a rare development.

EMBRYOLOGY

Cullen[4] reviewed the embryology of the umbilicus and urachus extensively in his text and the subject is also well reviewed by Begg.[1] The essence of these discussions is that the allantois, which is the fetal excretory tube, develops into the urachus. During the second or third month of fetal life, the bladder is formed when the common cloaca is divided by a developing septum. The anterior half becomes the bladder and the posterior half the rectum. At first, this bladder extends to the umbilicus, but as development proceeds, the upper half of the bladder narrows to form the urachus while the lower portion results in the urinary bladder. Because of this common origin, the urachus is lined with epithelium, but in the adult it becomes a narrow cord-like structure. One easily can see that cell rests along the course of the urachus would be possible. They are, as a matter of fact very common, and from these cell rests cysts can develop. It takes little imagination to visualize cells remaining in the urachus as a source of tumor. Since the primitive hind gut is the source of both the urachus and the rectum, it is not surprising that these tumors of the urachus are mucinous adenocarcinomas, which microscopically closely resemble such tumors of the rectum.

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PATHOLOGY

As indicated above, these tumors microscopically are irregular cystic spaces filled with a clear, homogeneous material which is mucin. The epithelial lining of these spaces lies directly on the underlying stroma without the presence of a tunica propria. The epithelium may be heaped up to form several layers and usually is high columnar with basal nuclei and mucin-secreting goblet cells. Grossly these tumors are solid with an irregular surface attached to the dome of the bladder and are covered superiorly by peritoneum. On cut section they have a glistening, gelatinous appearance with cystic areas of various sizes containing jelly-like material.

CLINICAL FEATURES

The mucinous adenocarcinoma of the urachus has been reported more frequently in males than in females, ranging from 26 to 83 years, but most common in the fifth decade. These patients usually present themselves with gross hematuria. This, however, is a late symptom caused by ulceration of the bladder mucosa. The presenting sign or symptom may be a suprapubic mass in or near the midline. Such tumors usually infiltrate and invade the adjacent peritoneum, pelvic organs, and bladder. Distant metastases are late manifestations. The usual life expectancy following diagnosis is two and one-half to three years. At the present time, the treatment of choice is radical excision of the tumor, including the dome of the bladder, the entire urachus with its underlying peritoneum, and the umbilicus.

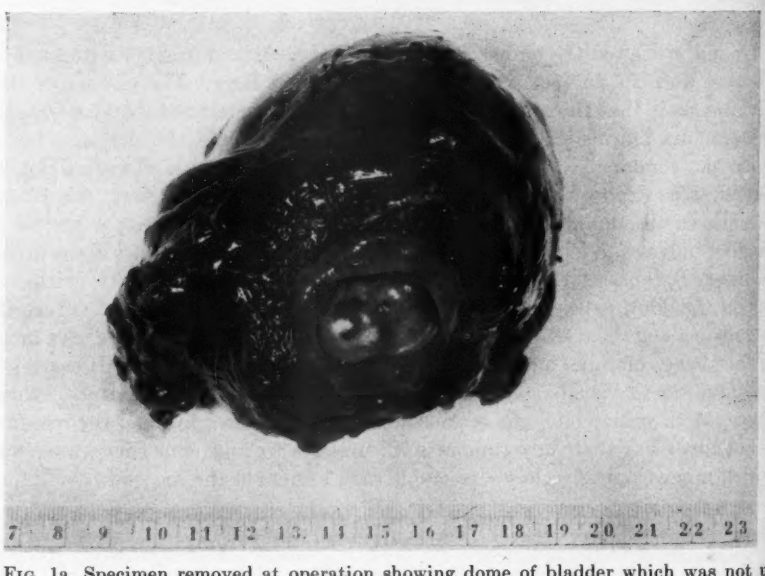

FIG. 1a. Specimen removed at operation showing dome of bladder which was not ulcerated.

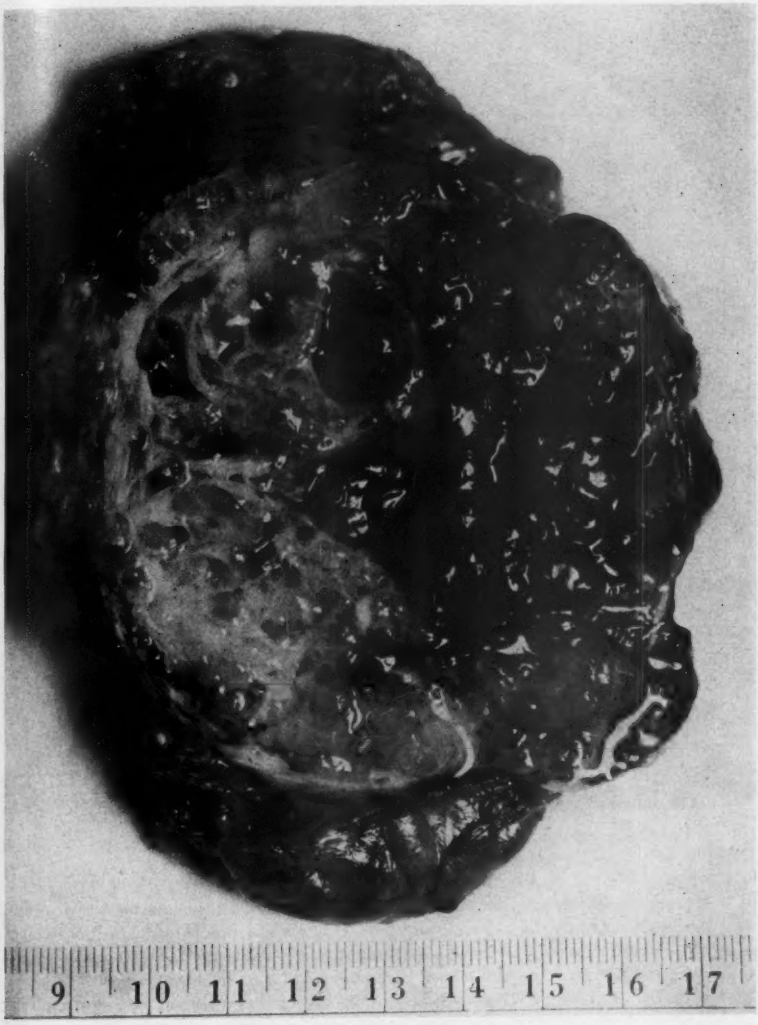

FIG. 1b. Cut section of specimen showing many cystic spaces filled with mucinous material.

Unfortunately, the diagnosis has in the past been so late that a long-term survival has not been reported.

CASE REPORT

A 43 year old white man, a former pugilist, was admitted to the Thayer Veterans Administration Hospital, Nashville, Tennessee, on Oct. 19, 1950 for repair of a left inguinal hernia. Prior to this time he had had no urinary complaints and has reportedly been in his

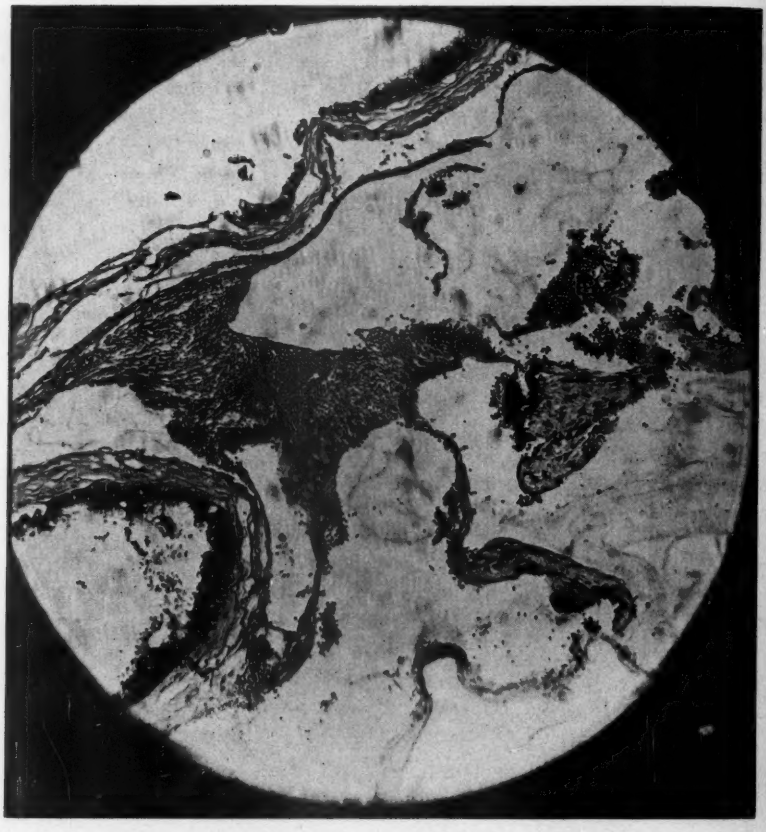

FIG. 2. Photomicrograph showing cystic spaces filled with mucin and lined by columnar epithelium including goblet cells.

usual good health. Physical examination, however, revealed a firm, nontender, suprapubic mass. Consequently, a barium enema and proctoscopic examination were done which revealed only evidence of an extrinsic mass pressing on the sigmoid. Cystoscopy showed a deformity of the dome of the bladder as though an extrinsic mass was present. There was no ulceration in the bladder. The clinical impression of the urologist was that this might represent a urachal cyst. Urinalysis was negative. Chest roentgenogram was normal.

On October 26, under spinal anesthesia, an exploration of the suprapubic area was done. A 9 by 11 cm. globular, irregular mass was found densely adherent to the sigmoid and dome of the bladder. The surface of the mass was covered with nodules containing a mucinous material (figs. 1a and 1b). Similar nodules were found scattered through the omentum. The lesion was peeled off the sigmoid colon and excised including the dome of the bladder and the omentum. The postoperative course was uncomplicated. The pathologic diagnosis was mucinous adenocarcinoma of the urachus and mucinous adenocarcinoma, metastatic, to the omentum (fig. 2). The tumor weighed 415 Gm. The patient was discharged from the hospital on Nov. 13, 1950 without complaints other than the presence of the inguinal hernia for which he had presented himself. He returned to the hospital in six months demanding to

have the hernia repaired. This was done in the usual manner and a metastatic nodule was found in the hernial sac. Digital examination of the peritoneal surfaces through the hernia sac revealed many small peritoneal nodules.

He was readmitted on Aug. 13, 1951 at which time he had no specific complaints other than a weight loss of 15 pounds. Examination revealed a rectal mass which appeared to be extrinsic to the rectum. During the next 10 months he gradually lost weight and his abdomen filled with many nodular masses. He died on June 27, 1952. This was only 20 months after

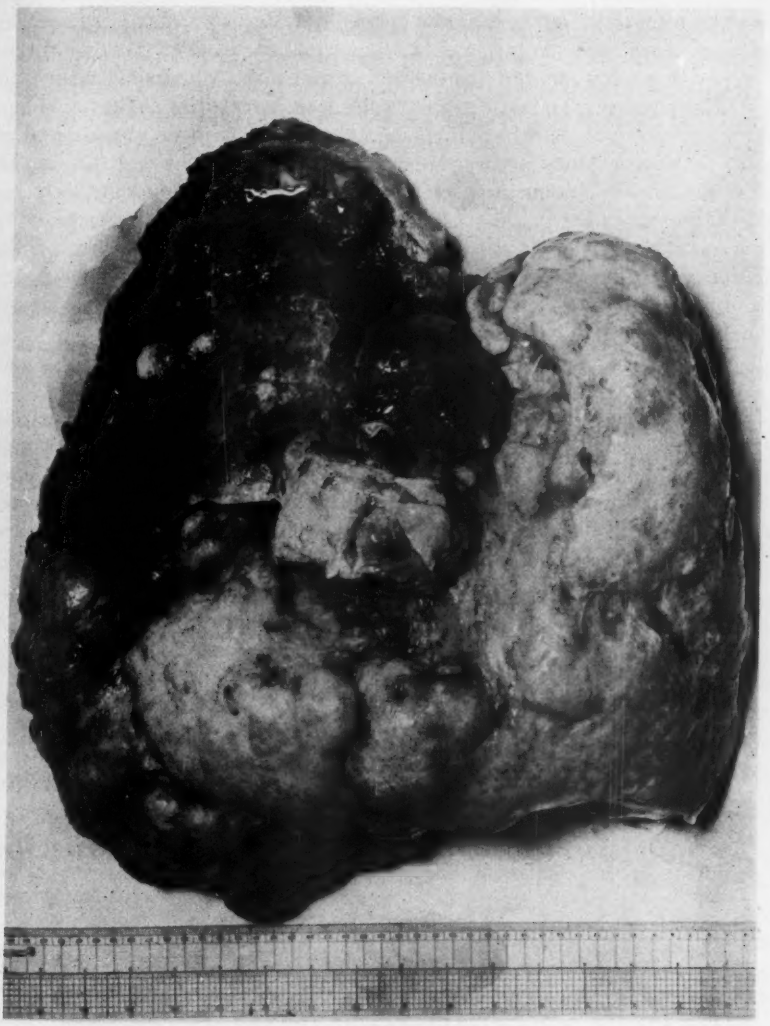

FIG. 3. Abdominal contents at autopsy showing the massive peritoneal metastases. The liver is seen in the upper left portion of this photograph.

his original exploration. Autopsy revealed massive, gelatinous, nodular tumor filling the entire peritoneal cavity as can be seen in the illustration (fig. 3). There was no evidence of recurrence locally in the dome of the bladder. A pathologic study of the autopsy material showed the same type of tumor as had been originally removed. The final diagnosis was mucinous adenocarcinoma of the urachus.

DISCUSSION

As other authors have said, the most common presenting symptom in this disease is hematuria, but as has been pointed out, this is a rather late manifestation as it necessitates ulceration of the tumor into the bladder. This patient had no presenting symptom, but the presenting sign was a suprapubic mass found on routine physical examination. This is, also, a rather late sign as the tumor must be big enough to be palpable. Of course, this patient, because of peritoneal implants found at exploration, was hopeless from the beginning and this was well borne out by the subsequent course. Such a situation is common in this disease and the prognosis has in the past been very poor. As in most carcinomas, the signs and symptoms are late in appearing so that an early diagnosis with radical excision and subsequent cure are difficult. This seems particularly apropos for this tumor. One must, however, continue to think of it when the two signs of hematuria or suprapubic mass on or near the midline are present.

SUMMARY

The sixty-fifth reported case of mucinous adenocarcinoma of the urachus is presented with a brief review of the literature. This case fitted into the usual category of clinical features in that it was present in a man in the fourth decade and had as its presenting sign a suprapubic mass. As in the majority of such patients with this disease, the fatal outcome occurred less than two years from the time of diagnosis and definitive treatment.

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TREATMENT OF "THE FROZEN SHOULDER"

(CHRONIC ADHESIVE PERIARTHRITIS)

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Chronic adhesive periarthritis of the shoulder, commonly referred to as the frozen shoulder, is well known to most practitioners who deal with adults. The condition rarely if ever affects children. Not much is known of the true pathologic process in this condition. We believe that lesions of long standing in the supraspinatus tendon, with or without calcification, are the most frequent underlying cause leading to this chronic syndrome. Similar traumatic lesions in other parts of the shoulder joint may produce the same picture.

The purpose of this paper is to present only the opinions and practices of the author developed over a 20 year experience with this condition. The findings of others will not be discussed and no attempt will be made to present and evaluate the many concepts developed by other authors. Several observations have been made and conclusions drawn, based upon what appears to be well grounded conceptions. Whatever the underlying disease process is, it seems to be the result of trauma, either recent or remote. It occurs in adults after many years of normal or abnormal use of the shoulder. There frequently is a history of acute trauma, such as a fall or throwing some light object. We believe that the condition is not the result of localized infection within the joint; is not related to remote foci of infection or to an acute infectious process.

Bursitis, whatever that term implies, is oftentimes the forerunner of the stiff shoulder. We believe that during this process the surfaces become inflamed; the opposing inflamed surfaces become adhered to each other, and if the fixed position of adduction is maintained for a long enough period, there develop adhesions between the opposing surfaces. This finally leads to a well formed adhesive band or bands of scar tissue. At this stage the well known state of *frozen shoulder* is established. Such a shoulder is painful on motion and the natural reaction of the patient is to keep the shoulder at rest with the arm at the side; attempts to move the shoulder cause pain; pain produces muscle spasm and spasm further splints the joint. This process produces a vicious cycle and before many days have passed the patient is almost incapacitated.

The usual symptoms are: (1) pain in or about the *cap* of the shoulder; (2) pain in or about the insertion of the deltoid muscle on the humerus; (3) vague nondescript pain or aching which may radiate down the arm, forearm and into the hand; (4) in advanced stages, the hand and fingers may appear to have the circulation disturbed. Joints of the hand become stiff, thereby leading to the condition frequently referred to as, *shoulder, arm, hand syndrome*. Frequently the condition

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is confused with the cervical disc syndrome, however, to the careful observer the differential diagnosis should not present a problem.(5) The patient finds it impossible to carry out the ordinary, everyday activities of life and sleep is greatly disturbed.

On physical examination the examiner often finds: 1. The entire musculature of the shoulder, arm and forearm is smaller than the opposite side. 2. All movements of the shoulder joint (a) abduction, (b) external rotation, and (c) internal rotation; are restricted (fig. 1). 3. An observation which to our knowledge has not been reported before is that in the acute stage, there often may be felt a

FIG. 1. Miss G. E. C. Acute bursitis, four days duration, initial examination, maximal reach, exquisitely painful.

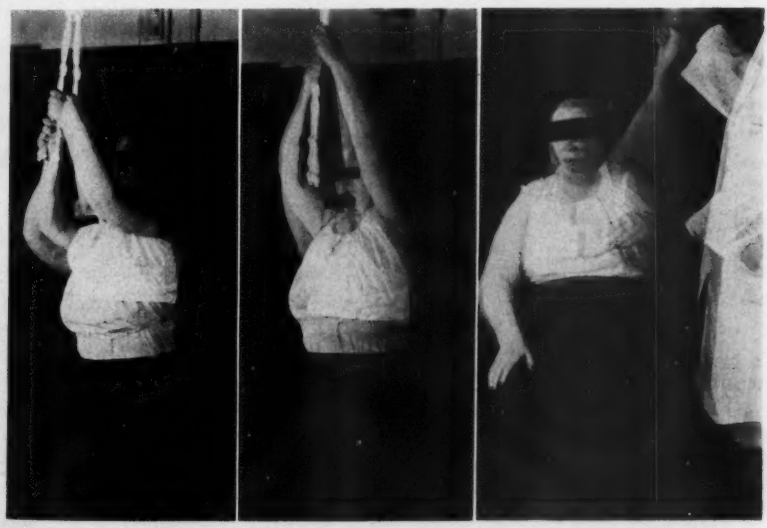
cold spot on the *cap* of the shoulder when compared with the normal shoulder. This is observed when the palms of the examiner's hands are placed simultaneously on the cap of each shoulder. It appears to represent a local vasospasm over the painful bursa or supraspinatus tendon. This is a frequent observation and it is not readily explained. It may be called the *cold spot* sign in the acute shoulder. 4. There may be apparent weakness in the muscles about the shoulder and arm. This is not true weakness or paralysis but reflex inhibition due to pain. 5. The vasospasm in the hand may lead to color changes and the skin may be glazed.

Roentgenographic examination always should be made. Two exposures are sufficient: (a) one should be made with the humerus in neutral rotation (anteroposterior with the forearm across the abdomen). (b) anteroposterior with the

humerus in external rotation as far as possible. One may see the shadow of a calcium deposit in a tendon; most often in the supraspinatus tendon, and sometimes evidence of bone atrophy or calcium absorption at one or more areas in the head of the humerus. We almost never see evidence of absorption or thinning in the articular cartilage of the head of the humerus.

TREATMENT

Many forms of treatment have been suggested in the past. Some of them will be mentioned only to be condemned. 1. Injections of various substances into the muscles or veins; such as, B12 and salicylates, which can act only by altering the body as a whole and cannot be expected to restore motion to the frozen shoulder. 2. Deep radiation therapy may occasionally favorably affect the very acute, early stage of bursitis, but it is of questionable value and, even in this early stage, it usually fails. Radiation therapy should *never* be given in the established state of frozen shoulder. It can lead only to disappointing results and may delay proper definitive therapy for too long a period by producing a false sense of security and hope. 3. Cortisone or ACTH given systemically can scarcely be expected to alter a condition in the shoulder which is traumatic, and this treatment is never justified. 4. The injection of hydrocortisone into the shoulder

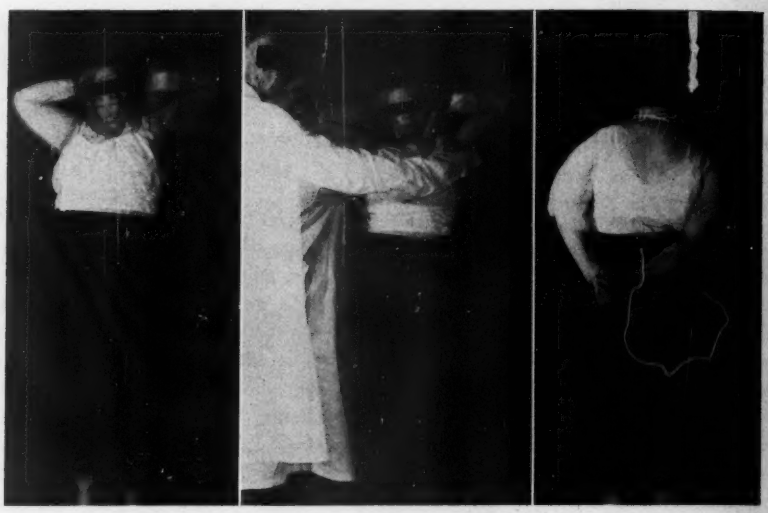


(a) (b) (c)

FIG. 2. (a) Same patient, exercise I with a double exposure. The patient grasps a stable object at maximal reach, using unaffected hand to aid painful side. Patient then *squats* as far as pain will permit. She rises and repeats this squatting exercise, producing forceful pull on the stiff shoulder. Repeat 10 to 15 times every 30 minutes.

(b) Same patient, exercise I. Double exposure showing increase in maximal reach after a few exercises.

(c) Same patient, exercise I. Double exposure showing the stretching exercise being carried out forcibly. Repeat 10 to 20 times each session, several sessions each day during acute stage.



(a) (b) (c)

FIG. 3. (a) Same patient, exercise II. Double exposure showing shoulder joint being stretched into external rotation and extension by patient's own active efforts. Repeat 10 to 20 times at each session every 30 minutes during acute phase.

(b) Same patient, exercise II. Double exposure showing the external rotation and extension exercise being assisted. This is painful and must be forced further by the attendant after the patient's efforts have accomplished their maximal range in this direction. Repeat 10 to 20 times every hour during acute stage.

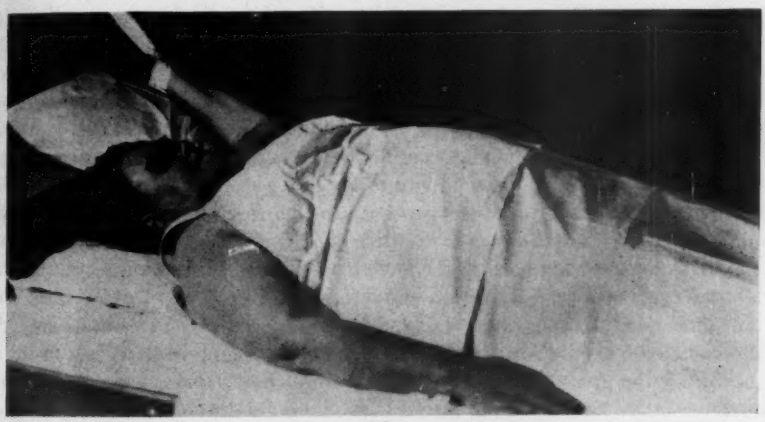
(c) Same patient, exercise III. Double exposure showing patient carrying out forceful internal rotation exercise to shoulder joint. Using the normal right arm as the source of power, the hand is pulled up the back as far as possible and lowered, to be pulled up again with force. Repeat 10 to 12 times every 30 minutes in acute phase.

joint or bursal region has proved disappointing to the author. We have seen patients in whom the accidental injection of this drug into the tissues has led to severe degrees of necrosis at the site of injection. 5. Heat, massage and bland applications may allay symptoms temporarily but do not affect a lasting change in the shoulder. 6. The use of narcotics is dangerous. 7. The generally practiced methods of physical therapy are not enough; for example, *finger climbing* of the wall and the swinging exercise in pendulum fashion are not sufficient to force movement in a stiff shoulder.

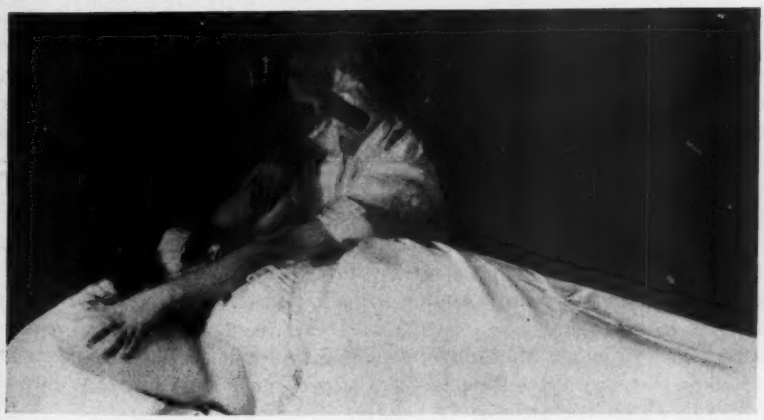
The author has found a few very simple and direct methods of treatment to be effective in the vast majority of patients.

1. The acute early stage of bursitis can be successfully managed by *three passive stretching exercises* which progressively increase and constantly maintain an increasing range of motion in the shoulder joint. These maneuvers are usually carried out by self-induced passive exercises in three directions, abduction (fig. 2, a and b), external rotation (fig. 3, a), and internal rotation (fig. 3, c) of the humerus on the scapula. If the threshold of pain is high, the patient will tolerate the increased pain of the initial exercise and proceed to force the movement in

spite of pain. If the threshold of pain is low, then the exercises should be carried out by the physician, his assistant, or some member of the patient's family who will not hesitate to push the treatment past the stage of pain, (fig. 2, c, fig. 3, b, and fig. 4, b). If the pain is too severe, some help may be obtained from medication such as codeine and aspirin given regularly for a few days. As a rule, the improvement is so marked in two or three days that the patient is willing to accept the increased pain in order to gain the expected relief. The exercises



(a)



(b)

FIG. 4. (a) Same patient, following manipulation under anesthesia, the hand is tied to head of bed by a soft gauze rope for 12 to 24 hours. This prevents the raw surfaces of torn adhesions from lying approximated until they are covered by a fibrin clot. At this time, the three stretching exercises are started again before fresh adhesions fix the shoulder joint.

(b) Same patient, exercise II. Double exposure showing technic of assisting patient with external rotation and extension exercise while in bed. Patient is encouraged to maintain this position as much as possible for 2 to 3 days following manipulation.

should be repeated *every 30 minutes* during the waking hours for the first few days; less frequently as improvement takes place. When the acute early stage of bursitis is treated in this manner, the results are nearly always gratifying.

2. If the acutely painful shoulder is found by roentgenographic examination to have a deposit of calcium, or if one can localize a single area of extreme tenderness by palpation, this area should be *needled*. This does not mean irrigation or aspiration for we believe that one cannot effectively wash out the calcium. The proper technic for *needling* is as follows: Using a small hypodermic needle one should first inject 1 per cent procaine into the skin over the most tender spot and then insert a no. 18 needle deep into the tissues, injecting the agent as the needle proceeds toward the calcified area and on down to the underlying bone. This will usually produce a palpable effect as the needle pierces the calcium deposit. Two to 4 cubic centimeters of the agent are injected into the depths of the calcium mass. This produces complete anesthesia of the painful area. After a few minutes, multiple needle punctures are made in the area previously found to be tender or localized by roentgenogram or fluoroscopic examination. Beginning at the center, we then make multiple needle puncture holes in the calcified mass. In order to assure oneself of effective needling, one should insert and withdraw the needle through the lesion many times in each of eight radial directions from the central puncture hole, making about a dozen punctures in each of the eight radii. The needle is withdrawn only from the deep lesion and not from the skin during the procedure. It is reinserted from the subcutaneous level in each new direction. After the radial multiple needle holes are made in the lesion, we then make several puncture holes in a circular direction by the same withdrawing and reinserting technic, each time pushing the needle down to the bone. Often a small amount of calcium flakes can be aspirated into the syringe, but this does not represent a significant portion of the calcium content of the lesion. It is our belief that pressure in the lesion is in this way relieved, and the trauma caused by the needle is followed by a hyperemia which rapidly absorbs the calcium deposit. Occasionally the calcium deposit is so large and of such long duration that one may be justified in the open operative removal of the lesion. In our experience we have found it desirable to operate upon very few patients.

After a thorough needling is done and while the shoulder is still pain free from the local anesthetic, the joint is carried through its full range of motion in all directions. Finally very firm pressure is made directly over the lesion with the thumb so as thoroughly to disperse the contents of the lesion into the surrounding tissues. The patient is then instructed in the technic of self-induced passive stretching exercises to the shoulder joint as previously described. The daily use of heat by an electric pad may be helpful.

This brings us to the stage of chronic adhesive periarthritis or, *adhesive capsulitis*. This condition is a most vexing problem and may produce many months of disability. Fortunately this syndrome tends to be self-limited. The author has never observed the condition to go on to a true bony ankylosis, but the fibrous ankylosis can be just as crippling and far more painful. The chronic stage of the condition with fibrous ankylosis should be dealt with first by the strong passive

stretching exercises described above. In some patients we must resort to more effective measures to mobilize the stiff joint than can be tolerated by the unanesthetized patient. At this time, we proceed to carry out forceful manipulation under general anesthesia.

TECHNIC FOR MANIPULATION UNDER GENERAL ANESTHESIA

Pentothal anesthesia is used and only three to five minutes are required for the manipulation. As soon as the patient is asleep, the operator stands on the side of the affected shoulder. He grasps the humerus as near the axilla as possible, using the right hand for the patient's right humerus or the left hand for the patient's left humerus. The opposite hand of the operator is placed on the top of the shoulder with the heel of this hand over the acromion. In this way, a very short lever of the humerus is used and the risk of fracturing the atrophic bone is reduced. An assistant stands on the opposite side of the bed. The assistant grasps the lateral border of the scapula with the fingers as his hand and forearm lie beneath the patient's chest. This hand of the assistant effectively stabilizes the scapula. With the scapula thus fixed firmly by the hands of the operator and his assistant, the humerus is forced first into complete abduction, and with this movement the operator may hear a loud snapping noise. The lever hand is then changed to grasp the forearm which is flexed to a right angle at the elbow. Using this lever the humerus is forced into both external and internal rotation. These forceful movements are repeated until a full and complete range of motion is obtained in all directions. There may be several rather loud snaps produced during the procedure.

When the manipulation has been completed, the hand is tied by a light gauze rope, made from a roll of bandage, around the wrist to the head of the bed, holding the shoulder in complete abduction and external rotation (fig. 4, a). Narcotics are usually necessary for the first day and night. The following day, the patient is allowed to get out of bed, and again, he is *immediately started on the self-induced three strong passive stretching excercises* described above. He must continue to practice the exercises of forceful passive abduction, external rotation and internal rotation for several weeks or even months before risking the natural tendency to allow the shoulder to remain at rest when it is painful. Any continuing or recurring pain must be a signal to again force the excerises even more diligently.

SUMMARY

A simple and effective plan of dealing with the problem of the stiff painful shoulder has been presented.

BIRTH INJURY OF THE CERVICAL SPINE PROUCDING A "CEREBRAL PALSY" SYNDROME

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The heterogeneity of the clinical syndromes which are included under the diagnostic rubric of *infantile cerebral palsy* presents a formidable problem in nosology. In a recent publication on the pathology of some of these conditions, Wolf[16] commented upon the necessity for gaining information which might result in more significant therapeutic and preventive measures. Certainly such an approach would be more fruitful than an endless compilation of all the pathologic processes which might damage neural mechanisms during the prenatal, natal, or postnatal periods.

No discussion of this subject should be undertaken without acknowledging the important and fundamental contributions of Crothers, Ford and Putnam.[2-5, 9, 10] It is particularly relevant that these workers have focussed the attention of neurologists, surgeons, and pediatricians upon the spinal birth injuries which previously had been of interest largely to obstetricians and pathologists. A recent case report by Alexander, Masland, and Harris,[1] with operative and autopsy findings, stresses the need for discovery of remediable lesions at a stage when therapy might be effective. Since the inherent contradiction of a term such as aleukemic leukemia has not been rhetorically repellent to clinicians, it might be appropriate to present the following report as a case of noncerebral cerebral palsy.

CASE REPORT

J. S., a 4 year old boy, was seen on March 25, 1953. The mother complained that he had never walked. Apparently he was the product of a full term uneventful pregnancy. The mother had been entirely well, and this was her only pregnancy. She became aware of fetal movements after about 4½ months of gestation, and these persisted until term. Labor began spontaneously and continued for about 24 hours. It was the mother's impression that her labor was considered difficult and that it was terminated by a breech delivery. The physician who delivered the child has written us that the infant was delivered by version and extraction following a persistent posterior occiput presentation and that no difficulty was encountered. Respirations were spontaneous and continued normally. The birth weight was approximately 7 pounds. There was no history of neonatal seizures. Although he took his feedings well, it was noticed during the first few days of life that there was little movement of any of the extremities. He gained weight in a satisfactory manner, and growth was not retarded, but he did not sit alone until he was 18 months old. He never held

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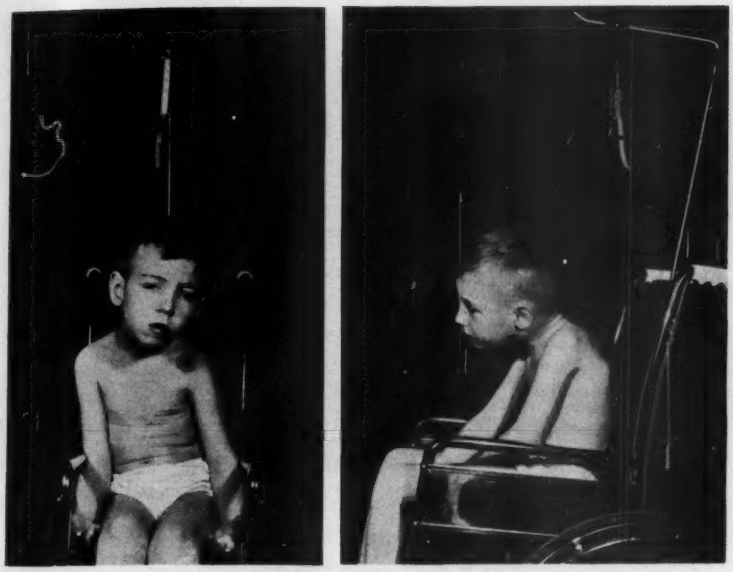

FIG. 1. Typical attitude without head support

his head up well. There was no history of sphincter disturbances. He began to talk at the end of his second year, but his speech had never been distinct.

General Physical Examination: He was a well developed boy who exhibited a decidedly rounded back as he sat with his head toppled forward, the chin resting on the chest (fig. 1). The respiratory movements of the thorax appeared normal. The tonus in all extremities was increased and there was generalized weakness. He was unable to execute fine movements of the hands, and he could not raise either hand to his mouth or grasp a spoon. No contracture or muscle atrophy was apparent. He exhibited no abnormal involuntary movements and appeared generally passive as he slumped forward in the chair. When placed on his feet he was unable to stand and gradually slipped to the floor in a sitting position. A pronounced kyphosis was noted in the region of the midcervical spine. The nuchal ligament was clearly outlined as it supported the head in the flexed position. The cervical spine was easily returned to the fully extended position by supporting the head in an attitude of extension.

Neurologic Examination: He was a very alert boy whose speech was indistinct and nasal. There was no element of dysphasia. He answered questions readily and executed simple commands well. The lower jaw deviated to the right when the mouth was opened widely, and he was unable to protrude the tongue completely. No involuntary movements were discernible. He did not grimace, and there was no posturing or athetosis. The pupils and ocular fundi were normal. No nystagmus or ocular muscle imbalance was noted. Muscle tonus was generally increased, particularly in the lower extremities. All extremities exhibited moderate and diffuse weakness, as previously described, the right upper extremity being the most involved. The deep reflexes were hyperactive and symmetrical with a bilateral plantar extensor response. There was unsustained left patellar clonus. No signs of meningeal irritation were detected. Although accurate sensory testing was probably not reliable, no gross changes were apparent on testing with pin prick. Sensation over the face seemed normal, and the corneal reflex was bilaterally brisk.

Roentgenologic Examination of the Cervical Spine: V. U. H. March 25, 1953 Cervical

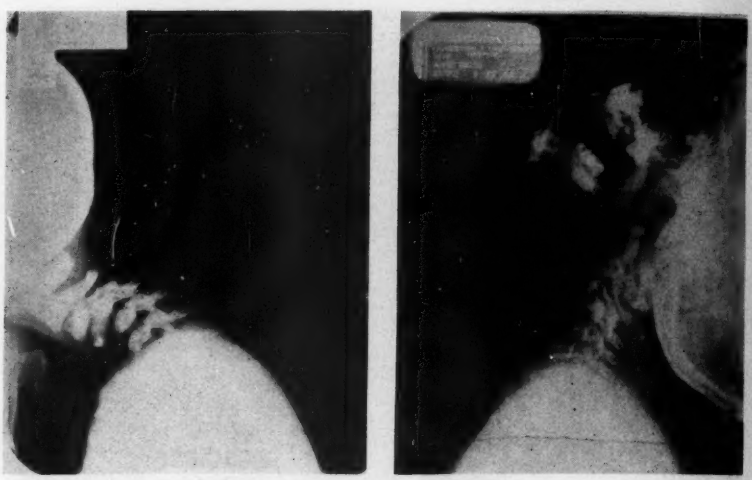

FIG. 2. Roentgenograms made March 25, 1953. Flexion and extension position from the lateral view of the cervical spine.

Spine: "The lateral projections were made in the neutral, flexion, and extension projections (fig. 2). In all views, the first three cervical vertebrae are in a position slightly anterior to the normal. There is a fracture of the vertebral body of C-4, and there is a posterior dislocation of C-4 equal to one-half of the normal anteroposterior diameter of the body. The fourth vertebral body is markedly elongated, apparently due to traumatic compression. The normal anteroposterior diameter of the cervical bodies is about 1.5 cm. At this distance from the posterior margin, there is a translucent vertical line of about 1 mm. in thickness, bordered by slightly sclerotic zones. The total anteroposterior diameter of this fourth cervical body is 2.3 cm. Anteriorly, there is a triangular segment of bone measuring approximately 4 mm. on each side. This segment is denser than the remainder of the body, suggesting a separate fragment which may be undergoing revascularization. Marked angulation of the cervical canal occurs between the 3 and 4 C. levels. The posterior margin of the body of C-4 makes an angle of about 45 degrees with the horizontal. The posterior margins of C-5, 6 and 7 are approximately vertical. The anterior margins of the 5th and lower cervical vertebrae approximate the posterior margins of the 3rd and upper cervical bodies.

The above description applies to the neutral position. In extension, the posterior margin of the 4th cervical vertebra is in approximately normal relation to that of the bodies of C-5, 6 and 7, while in flexion the posterior margin of C-4 approximates the appearance of the neutral position.

Conclusion: Anterior dislocation of the first 3 cervical vertebrae. Marked posterior dislocation of the 4th cervical vertebra with marked angulation of the cervical canal between C-3 and 4, and marked posterior curvature of the cervical canal between C-4 and 5 levels in neutral and flexion positions. Compression fracture of C-4 to a marked degree in its anterior portion." (H. C. Francis, M.D.)

Subsequent Course: The child was fitted with a head supporting brace to facilitate gait training, and a canvas head halter was used to maintain head position while sitting in a chair (fig. 3). He was taught to stand with the aid of parallel bars, and his general strength improved greatly following six months of intensive physical therapy and occupational therapy, with the emphasis on gait training and coordination exercises. He became able to feed himself and his speech was much more distinct. This improvement was at-

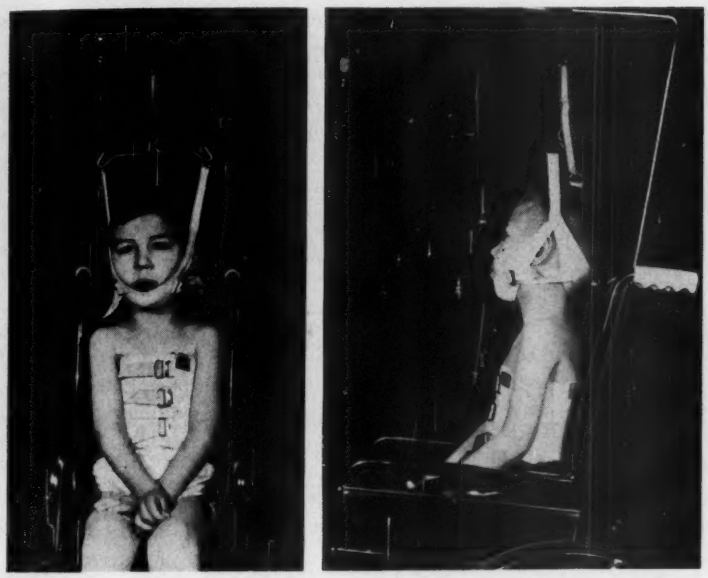

FIG. 3. Typical attitude with spring type head support and corset

tributed to increased opportunity for conversation with his therapists and with other children, since no speech therapy was employed. No change has occurred in the neurologic signs.

In order to achieve permanent stability, it is planned to do a fusion of the hypermobile portion of the cervical spine. This surgical procedure has been deferred because it will be less hazardous and more easily accomplished when the patient is a few years older. It does not seem desirable to delay the necessary rehabilitation measures at this time. To delineate further the changes in the cervical spine a myelographic study would have been of interest, but it was not considered advisable to incur even the slight risk of such a procedure.

DISCUSSION

Three major types of spinal birth injuries, each differing in the mechanism of production, have been recognized.

1. *Displaced fractures and dislocations of the spine (usually cervical).* Breech delivery with excessive traction and angulation of the cervical spine was demonstrated in postmortem and anatomic preparations by Stoltzenberg[14] to result in a sequence of regular changes. There occurred first, a luxation of one facet joint, second, separation of the interspinous and interlaminar ligaments, and finally disruption of the anterior and posterior longitudinal ligaments allowing separation of the vertebral bodies through epiphyseal lines with displacement. Similar findings were reported by Pierson[12] in 1923 when he found vertebral fractures in 17 of 36 cases of neonatal or natal deaths following breech delivery. The postmortem studies of these cases suggest that the lesions in the spinal cord might

range from simple contusions and hemorrhagic areas to complete transection of the cord with massive intraspinal and intracranial hemorrhage.

2. *Traction injuries without roentgenologic changes.* Attention was drawn by Crothers[2] in 1923 to the possibility of survival following spinal cord birth injury when he reported the clinical findings in 5 representative cases. Two years later, Ford[9] published a report of 5 similar cases with one necropsy. In none of his cases was there roentgenologic evidence of vertebral injury. It has been pointed out by most authors that, in the newborn infant, the vertebral axis is sufficiently elastic for the spinal cord to sustain damage without gross disruption of the articulations, and the cord damage may occur at any point from the medulla to the cauda equina.

Quantitative estimation of the longitudinal traction required to produce dehiscence of the vertebral articulations has been a subject of controversy. Duncan[6] found that 105 pounds of traction produced separation of these articulations and 120 pounds resulted in decapitation. Rokitansky is quoted in Ehrenfest's[7] exhaustive study as having stated that longitudinal traction along the spinal axis was of no significance as a cause of spinal birth injury. Stoltzenberg[14] while referring to one study in which 1000 pounds of traction was necessary to injure the cord, reported that a much smaller force, improperly applied, could produce great damage.

In an experimental study which has not been completed, one of us (T. F. P.) has investigated the elongating effect upon the cervical spine of small degrees of longitudinal traction. In this study no attempt has been made to produce disruption of articulations, but rather, to measure by teleroentgenograms the distance from the foramen magnum to the superior margin of the second thoracic vertebra as traction force is increased. In one stillborn infant the first 15 pounds to be applied produced a distraction of 5.0 mm. while additional force up to 45 pounds resulted in no further elongation. These preliminary studies suggest that torsion or lateral deviation must play a determining role in the production of spinal injury since longitudinal traction alone does not result in any extreme elongation of the vertebral column.

The problem which has obscured the evaluation of the patients who survive traction type injury of the spinal cord has been the absence of confirmatory roentgenographic change and the necessity of reliance upon an incomplete history. In establishing such a diagnosis, it might be well to adhere to the diagnostic criteria set forth by Ford, Crothers, and Putnam[5] who required: (1) that the disability be noted as soon after birth as an adequate examination could be conducted, (2) that amyotonia congenita, myelodysplasia, tumor, and infection be considered, (3) that the disability not progress after the acute stage, and (4) that the force employed during delivery might have caused the supposed injury. The difficulty in establishing the last criterion is too apparent for further comment, for as these authors state, "No obstetrician ever uses what in his judgement is unjustifiable force." Fay[8] has discussed the difficulty of differentiating the *high spinal spastic* from *cerebral palsy*, and emphasized the importance of this differential diagnosis.

3. *Intrauterine malposition of the fetus.* A condition which is well recognized by obstetricians is the *flying fetus* intrauterine position (Knowlton[11]) or the opisthotonus fetus. In these cases, the entire spine of the fetus in utero is in extreme extension. Taylor's[15] patient was delivered by cesarean section, and a dislocation of the third and fourth cervical vertebrae was demonstrated roentgenographically on the sixth and eighteenth day of life. It is of great interest that in his patient the position of extreme extension confirmed roentgenographically, resulted in a flexion type dislocation with forward displacement. One explanation for the paradoxical conversion of an extension injury into a flexion deformity assumes that the complete relaxation of all the supporting soft tissues of the cervical spine permits hypermobility in all directions. When subsequent patients are studied, it would be valuable to examine roentgenographically the cervical spines in flexion, extension, and in the neutral position.

In the patient who has been presented, as in the one described by Alexander, Masland, and Harris,[1] the pronounced motor impairment without seizures, athetosis, or retardation suggested that the lesion was not intracerebral. These 2 patients are also similar since both presented roentgenographic evidence of spinal derangement, a finding which is unusual among the few infants with spinal birth injury who survive the neonatal period. It must also be added that in the case reported by Alexander and associates it was impossible categorically to designate birth trauma as the sole etiologic factor.

CONCLUSIONS

A case of cervical spinal cord birth injury with roentgenographic changes in a child who has survived to age 6 years is presented.

The major types of spinal birth injury are discussed.

The possibility of a spinal birth injury should be considered whenever the general designation of cerebral palsy seems appropriate.

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DUODENAL ULCER

It is generally agreed that duodenal ulcer primarily is a medical disease and that not more than 15 to 20 per cent of those treated will require surgery. There is not general agreement, however, on the type of operation that will uniformly give the best results. Subtotal gastrectomy (removing 75 per cent of the stomach), vagotomy plus gastroenterostomy, and vagotomy plus antrectomy (40 per cent resection) are the operations currently employed for duodenal ulcer. Surgical intervention in cases of duodenal ulcer should accomplish: (1) a cure of the present disease, (2) insure the patient against further ulcer development, (3) leave a stomach pouch which will enable the patient to remain well nourished and (4) protect him against the *dumping syndrome*.

Dragstedt, in 1943, revived the operation of vagotomy, which put the surgical treatment of duodenal ulcer on a physiologic basis. He found that a complete vagotomy would reduce hypersecretion to normal or below normal in over 90 per cent of cases; however, it soon was discovered that the results following vagotomy alone were not good because of ill side effects, and gastroenterostomy was added to enable the stomach to empty normally. Results following vagotomy and gastroenterostomy have been reported as comparing favorably with subtotal gastrectomy, but most series of cases reported show an incidence of jejunal ulcer in 5 to 6 per cent of cases. In recent years because of jejunal ulcer and ill side effects following both radical subtotal gastrectomy and vagotomy and gastroenterostomy, a number of surgeons have become interested in vagotomy and conservative resection as a method of attaining improved results.

This brings up the question, do vagal and antral hyperfunction coexist in the patient with duodenal ulcer? We have found, following vagotomy and gastroenterostomy—in spite of a negative response to insulin hypoglycemia,—that the concentration of free acid is diminished during the fasting state, but the volume of gastric juice still may be abundant. When these patients are stimulated by a test meal or with histamine, both the concentration and the volume of gastric juice may rise precipitously, closely paralleling the findings in patients with active duodenal ulcer.

At the turn of the present century, the antrum was demonstrated by Edkins to function as an endocrine organ capable of stimulating the fundic glands through the liberation of gastrin. This work subsequently has been confirmed by others. More recent experimentation has shown the antrum capable of producing excessive gastric secretion when transplanted into the wall of the transverse colon as a diverticulum. It is also of interest to note in the experimental animal that vagotomy coupled with antral extirpation offers protection against the Mann-Williamson ulcer in a high percentage of cases, whereas, vagotomy without antral extirpation offers protection to only a small number. The experimental work of Sauvage and Harkins serves to evaluate the relationship between the physiologic stimulatory mechanisms of gastric secretion and clearly shows the importance of the antrum in the genesis of ulcer in the experimental studies.

They suggest that the surgical management of gastric hypersecretion in patients with duodenal ulcer should include the removal of the accessible stimulatory mechanisms (vagal and antral), a procedure founded upon sound physiologic principles.

Radical subtotal gastrectomy reduces the hypersecretion by removing the hormonal phase and actually removing some of the parietal secreting cells and, if only a small pouch of stomach is left, the incidence of jejunal ulcer is decreased, but the incidence of troublesome conditions such as weight loss, anemia, and the *dumping syndrome* is increased. The operation does not appear to be based on sound physiologic principles because it does not remove the vagal stimulatory mechanism and it multilates an organ necessary to good health.

During the past seven years our experience with a series of 150 cases of vagotomy and antrectomy, (with a no loop posterior gastrojejunostomy) has shown us that results have been superior to subtotal resection or vagotomy and gastroenterostomy. Not a single case of jejunal ulcer has developed during a follow-up period of one to seven years. The patients have maintained their normal weight in well over 90 per cent; the incidence of *dumping syndrome* has been materially reduced, and they seem to be able to consume food in normal quantities without discomfort. Further careful clinical and follow-up studies will be required to evaluate fully the relative merits of this procedure. The morbidity and mortality rates are extremely low in this operation, the only deaths in this series being due to cerebral vascular accidents or coronary disease.

There appears at present to be a growing interest in vagotomy and conservative gastrectomy. Ransom and his group at the university of Michigan, in a small series of patients followed from two to three years, report results superior to those obtained with radical resection alone or with vagotomy and gastroenterostomy. Zollinger reports gratifying results over a short follow-up period. Harvey and St. John mention good immediate postoperative results in that their patients have not developed important symptoms of dumping and have been able to eat substantial meals and to maintain their weight.

It is hoped that further interest will be stimulated in this intriguing subject, as an adequate clinical experience will be necessary for proper evaluaton and assessment of the various operative procedures currently done for duodenal ulcer.

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